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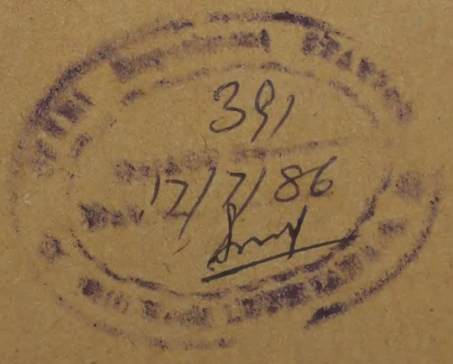

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Fast Atom Bombardment (FAB) Mass Spectrometry—Some Recent Advances

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The use of modern analytical instruments has opened many frontiers in chemistry and biochemistry. Of the various instrumental techniques, available for the identification and characterisation of complex biomolecules, mass spectrometry has played a major role. In recent years impressive developments in mass spectrometry have taken place resulting in an enormous growth in the number and kinds of compounds which can be studied with it. The present article deals with the latest technique in mass spectrometry, i.e. the fast atom bombardment (FAB), its applications and recent advances made in the area.

In mass spectrometry an electron beam of 70 eV bombards the neutral molecule of the sample in gas phase and in an electronic transition strips an electron to leave a positive radical ion M^+. This ion possesses excess energy and dissociates into fragment ions.As it requires volatilisation and ionisation of the sample many important types of molecules, specially biomolecules such as hormones, enzymes, peptides and nucleic acids etc., because of their thermal instability and low volatalisation could not be subjected to mass spectrometry. Attempts have been going on to circumvent this problem with varying degrees of both success and failure. One approach is to increase the sensitivity of the instrument so that measurable ion current can be detected even at extremely low vapour pressure. A trapped ion cyclotron resonance mass spectrometer was developed[1] that could detect vapour pressure down to 10^{-10} torr, a factor of 10,000 better than an electron impact mass spectrometer with direct sample inlet system. The other technique which is widely used in mass spectrometry is to prepare a suitable derivative of the compound. Compounds containing several polar groups (such as carbohydrates and peptides) have very low volatility and these can be modified chemically to non-polar derivatives having high vapour pressure than the parent molecule. Trimethylsilyl derivatives serve efficiently for the purpose, and can also be utilized for gas chromatography-mass spectrometry (GC-MS) technique. Recently, it has been shown that if a solid film of a peptide is deposited on a nonreacting surface such as Teflon, the vapour pressure of the peptide is effectively enhanced and vapourization can be effected at low temperature[2]. Chemical ionisation[3-5] is another promising technique in which quasi-molecular ions (M $\pm$1) are formed by reaction of the sample with generated ions such as CH_5^+, $C_2H_5^+$, $t\text{-}C_4H_9^+$ or NH_4^+.

Newer techniques

In the techniques mentioned above vapourization of the analyte is a prerequisite as the sample molecules must be injected into instrument in the gas phase before it is ionised. This has proved especially troublesome in cases of compounds of biological or biomedical importance because of their nonvolatile nature or thermal fragility. During the last decade a number of techniques have been developed to overcome the problem of analysis of such compounds. The basic approach is to desorb the ions directly from a condensed phase, solid or liquid. Such desorption techniques which have revolutionised the field of mass spectrometry are field desorption (FD), plasma desorption (PD), secondary ion mass spectrometry (SIMS), electrohydrodynamic ionization (EHMS), laser desorption (LD) and thermal desorption. The latest to join this impressive array of modern techniques is fast atom bombardment (FAB). With these techniques it is now possible to obtain mass spectra of compounds[6-8] with molecular weights above 12,500 and to obtain detailed structural information on compounds with molecular weights as high as 2800.

In FD technique[9-13] the sample is deposited on an emitter. The PD technique[14,15] utilizes energetic fission fragments from the decay of ^{252}Cf to volatilise and ionise a solid sample. The vaporized sample particles quickly form quasi-molecular ion. The technique is applicable to a wide variety of

compounds, including amino acids, moderately large peptides, nucleotides and natural products. Another widely used technique, the SIMS[16,17] is based on the use of ions of keV energy to energise the samples, usually in solid form but often mixed with a solid matrix. It also forms a sensitive method for elemental analysis. A relatively less common technique is the EHMS in which samples are dissolved in glycerol containing an electrolyte, and desorption takes place directly from solution under the influence of high fields without the application of heat[17]. In LD technique[18,19] the short pulse energy is provided by a laser. The method suffers from the disadvantage that tendency towards thermal degradation is greater in this technique than that in other desorption ionisation techniques. In thermal desorption[20,21] technique samples are introduced on a direct probe into the source and desorption of ions is achieved by heating the probe tip. The technique has been mainly used for inorganic analysis but has also found applications in analysis of organometallics.

Fast Atom Bombardment (FAB) Mass Spectrometry

This is one of the recently developed desorption ionisation techniques and has been successfully applied in determining the precise masses of molecular ions of thermolabile biologically active compounds with high molecular weights. It is especially applicable to the analysis of nonvolatile, polar and zwitterionic compounds. It has also provided structural information on many other classes of compounds.

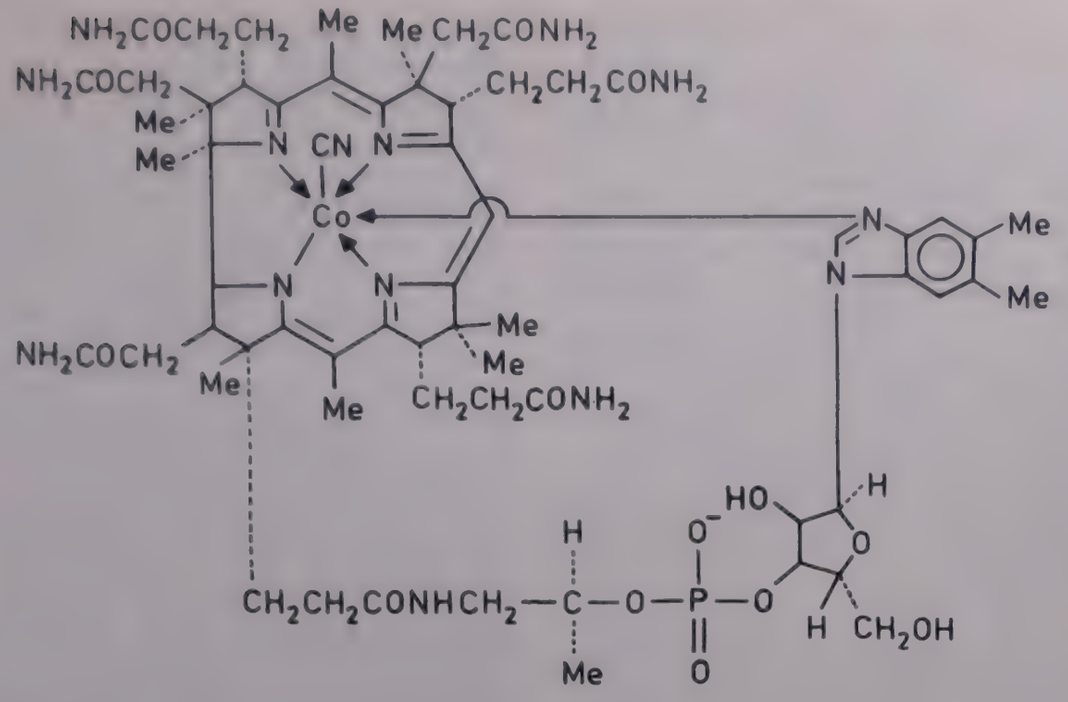
Developed[22-24] in 1981 FAB mass spectrometry employs a beam of fast neutral atoms of 2-8 keV energy, typically of argon as the primary particles. The source of fast atoms consists of a cold cathode discharge ion source and a collisional chamber. The discharge ion source produces a beam of ionised argon (Ar^+) of controlled energy in the range of 2-10 keV, which is focussed into the collision chamber containing argon gas under high pressure (10^{-3} to 10^{-4} torr). Resonant charge exchange occurs with little or no loss of forward momentum. This results in a particle beam emanating from the collision chamber which consists of a mixture of argon atoms (Ar) and ionised argon (Ar^+) (which escapes without being charge exchanged). The beam has the kinetic energy of the original ion beam. The ionic component is cleansed from the beam by a set of electrostatic deflector plates[22]. Although argon is a satisfactory inert gas, xenon gives about a three-fold increase in sample ion intensity, perhaps because of its greater mass and enhanced momentum[25]. The emerging fast atoms from the ion gun are made to enter the ion source of the spectrometer and are focussed on the sample in a glycerol matrix at an incidence angle of about 70°. Samples can be introduced into the system by first depositing them from solution onto a metal stage which is fixed to the shaft of a solid sample insertion probe. This can be introduced to the ion source through an axially mounted vacuum lock, in order to intercept the fast atom beam[22]. Ribbons of various metals and non-metals have been employed as the solid surface on which the glycerol matrix is placed[25]. Dispersion of the sample in liquid matrix like glycerol assists in maintaining the intensity of sample ions by regenerating the surface so that fresh sample ions can be extracted from it. With neat solid samples, ion current life-time is usually short. The importance of the viscous liquid matrix is almost universally recongnized and it is generally believed that solubility of organic sample in the liquid matrix, usually glycerol, is essential to obtain useful FAB mass spectra[26,27]. Other useful dispersants which can be used in place of glycerol are thioglycerol, polyethyleneglycols such as tetragol (tetraethyleneglycol) and its dimethyl ether (tetraglyme), sulpholane (tetramethylenesulphone), diethanolamine, diamylphenol, crown ethers and substituted ureas[25]. Recently, it has been reported that for compounds like tetraphenylporphyrin (TPP) and its derivatives dissolution of the sample in liquid matrix is not necessary to obtain a good FAB spectrum[28]. It can, however, be obtained by precipitating the sample *in situ* on the surface of a viscous matrix.

The ions produced from the sample by the sputtering mechanism are then accelerated to the normal spectrometer potential and pass into the analyzer region of the instrument. The type of analyzer and detector used in mass spectrometer appears not to be crucial for the success of the technique. A FAB gun can be attached to the ion source of an existing mass spectrometer with relatively little modification and expense.

The mass spectra obtained by FAB method give molecular ion species as $(M+H)^+$ in positive ion spectra and $(M-H)^-$ in negative ion spectra. Both the spectra can be obtained with equal ease, and often complement one another. Structurally sensitive fragment ions of the molecules are present in both the types of spectra. Metastable ions are observable in the spectra to assign fragmentation pathways[22]. The mechanism for ionisation process is still not clear[29] and controversy over the necessity of neutrality of the bombarding particles in the process still persists[30].

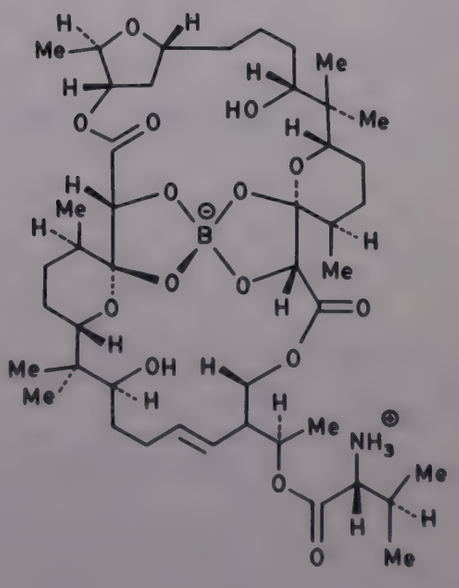
Applications

Fast atom bombardment (FAB) mass spectrometry has been recognized as the preferred method of ionisation for non-volatile and thermally unstable multifunctional molecules of biochemical and



(1)

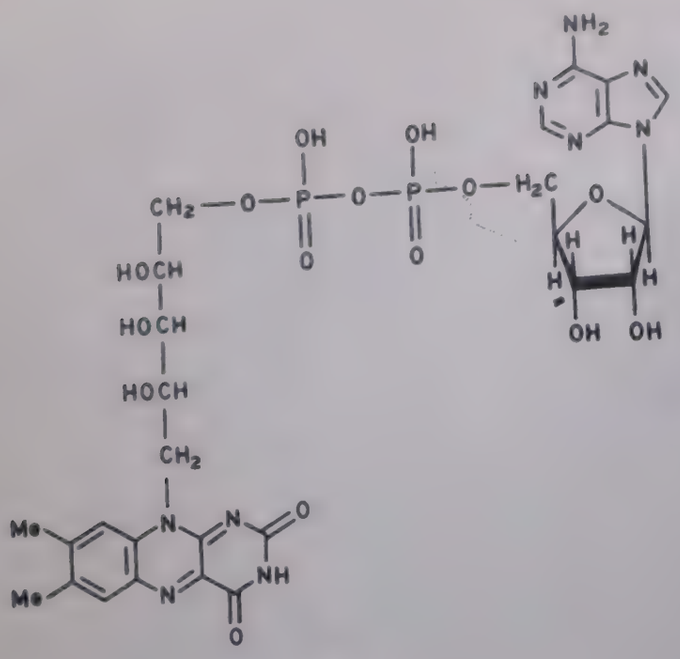
biomedical significance. The use of FAB has grown tremendously over the last four years and a great many compounds not amenable to ionisation by conventional mass spectrometric methods have now been analyzed successfully by this technique[31,32]. It has allowed mass spectroscopists to work more easily with larger molecules[6,33,34] with molecular weights as high as 10,000 to 12,500. The compounds that have been successfully investigated by FAB mass spectrometry are: oligosaccharides[35], antibiotics[29,36], oligopeptides[22], glycolipids[22], oligonucleotides[22,29], neurotoxins[22], leukotrienes[37], polyphenolic glycosides[38], chlorogenic acid[39] and platinum amine complexes[22] etc. Biopolymers such as glucagon[40], insulin[41,42], and proinsulin[43] have been weighed in the mass ranged of 3000-9390. Gastrins, the peptide hormones produced by gastric mucosa and mellitin, a peptide amide containing 26 amino acid units have also been successfully ionised[22].



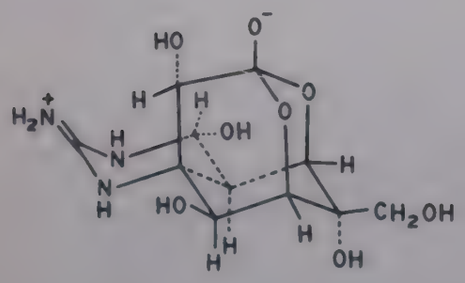
(2)

A milestone in the successful application of FAB mass spectrometry has been the FAB spectrum of vitamin B_{12} (cyanocobalamine) (**1**), a complex cobalt-containing molecule with modified porphyrin unit[44]. Recently, negative ion FAB mas spectrum of boromycin (**2**)[45], another organometallic of complex structure has been obtained[46]. An example where FD technique failed but FAB provided a facile analysis is provided by the antitumour drug guanosine monophosphate cross-linked by phosphoramide mustard[47]. The oligonucleotide, flavine-adenine dinucleotide (FAD) (**3**) has also been analyzed[22]. Other nucleotides where FAB has been applied are oxidised nicotinamide adenine dinucleotide phosphate and uridine diphosphoglucuronic acid, and ^{18}O-labelled analogues[46,48]. The other example where FAB has been applied using stable isotopes is the analysis of dipalmitoylphosphatidylcholine extract for amniotic fluid to which nonadeuteriodipalmitoylphosphatidylcholine has been added as internal standard[49]. Complex structures such as tetrodotoxin (**4**)[22] and leukotriene-C_4 (**5**)[37] have been studied.

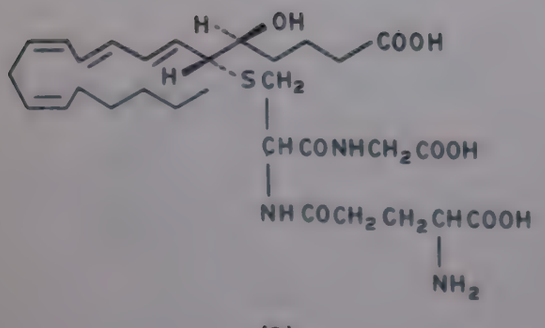
The FAB technique has been successfully applied in structure determination of large molecules through fragmentation. The fragmentation appears to occur in reproducible ways. Cleavage usually occurs where a



(3)



(4)



(5)

heteroatom is attached to a carbon chain. Thus when a compound containing a sugar is subjected to FAB, peaks of molecules with and without sugar are detectable. The mass difference between the peaks corresponds to 163, i.e. loss of a sugar ($C_6H_{11}O_5$) moiety. Thus it is possible to identify the sequence of oligosaccharide units, although, of course, distinction between isomeric possibilities such as glucose and galactose cannot be made. This has been applied in the study of two glycosphingolipids lactosylceramide and human erythrocyte globoside, and polyene antibiotics pyramycin and partricin-A[48]. Recently, structural deduction from fragment ions of FAB spectrum of a diphosphorylated fraction of lipid A lipopolysaccharide complex purified from a mutant of *Salmonella typhimurium* has been carried out[50].

Perhaps the most significant application of FAB mass spectrometry is in the study of polypeptides, where three types of information can be obtained from the spectrum. First, the molecular ion provides the molecular weight; secondly, ions at low masses are characteristic of individual amino acids; and thirdly and the most inportant, ions at intermediate masses provide the sequence of the amino acids in the peptide. Fragmentation takes place often at the CO – N bonds with charge retention on the amino terminal fragment. An excellent example is provided by the FAB spectrum of zervamicin 9C, a polypeptide antibiotic[25]. Hexahydrodidemnin-A, a sodium borohydride reduction product of didemnin-A, an antiviral and antitumor agent is the other cyclic depsipeptide studied[25]. High resolution mass spectrometry is also feasible with FAB, and atomic proportions of a fragment can be determined.

Some Recent Aspects

In cases where FAB ionisation does not form appreciable fragment ions, as in the case of the heptadecapeptide gastrin[51], tandem mass spectrometry[52] can supply substructural information; the molecular ion species separated by the first mass analyzer (MA – I) is made to undergo collisionally activated dissociation (CAD) producing fragment ions which are mass analyzed in MS – II[53–56]. Amster and McLafferty[57] have reported the application of tandem mass spectrometry in characterisation of artifact peaks in mass spectra of FAB ionisation. There are reports of occurrence of such spurious peaks in FAB mass spectrum[58,59]. Such peaks can be misleading when interpreting the FAB spectrum. These peaks can be individually characterized by further measuring their CAD spectra. The application of this latest technique has been illustrated by the spectrum of vitamin B_{12}. The FAB spectrum of vitamin B_{12} reported by Barber *et al.*[44] exhibited clusters of ions having higher mass values, although lower abundance, than the molecular species. A recent study by Amster and McLafferty[57] on the FAB spectrum of vitamin B_{12} (molecular weight 1354) also showed a *m/z* 1388 peak, the abundance of which grew at the expense of $(M + H)^+$ with continuing bombardment. The secondary mass spectrum of *m/z* 1388 produced by CAD indicated that it was formed by intermolecular transfer of a cobalt atom from one molecule to the phosphate group of another. Tomer *et al*[60] have employed a combination of FAB and tandem mass spectrometry for determining the molecular weights and amino acid sequences of cyclic peptides,

Recently, McCrery *et al.*[61] have obtained mass spectra of alkyltriphenylphosphonium halides using FAB coupled with tandem mass spectrometry. Alkyltriphenylphosphonium salts are used frequently for the synthesis of alkenes from carbonyl compounds in Wittig reaction[62], an important step in natural product synthesis[63]. The technique has also been applied successfully to the analysis of anionic[64] and cationic[65] surfactants. Disodium palmoate and its isomer have been identified[66].

This technique has also been utilized to obtain the accurate ($\sim$1 ppm) mass measurement of the ions generated[67]. Cotter *et al.*[68] have recommended FAB as a possible approach to high molecular weight unknowns and mixtures since the major features, particularly the molecular ions, can be quickly recognised from a few scans over a wide mass range and important region can then be examined at high resolution. This approach has been used to determine the molecular weights of mouse epidermal growth factors. The problem of the accuracy of isotopic abundance ratios obtained for FAB-produced ions has been minimised. Isotopic patterns in the molecular ion region for several classes of compounds were determined in both the positive and negative ion mode. In the course of evaluation, desorption of significant amounts of $(M+2H)^+$ and $(M+3H)^+$ was found[69].

Chang *et al.*[70] have reported a method for obtaining mass spectra of TLC spots by FAB mass spectrometry. The adsorbed materials, including those that are non-volatile or thermally labile, can be ionised while on adsorbent i.e. without elution. Recently, Stroh *et al.*[71] have described the technique of liquid chromatography/FAB mass spectrometry using a moving belt interface to observe pseudomolecular and fragment ions of polar compounds. Applications to a series of peptides, including the underivatized hexadecapeptide, antiamoebin-I (mol. wt. 1669), a mixture of emerimicins (zeravemicins) IIA and IIB (mol wts 1823 and 1837), and a mixture of tetra- to nona-peptides obtained by partial hydrolysis of antiamoebin-I were also described[71].

Campana and Freas[72] have reported a novel ionisation method involving a combination of chemical ionisation with FAB mass spectrometry which gives significantly enhanced sensitivity and selectivity over the FAB technique. The use of this new ionisation method has led to the enhancement of the molecular ion through various ion-molecule interactions which include charge exchange, proton transfer, association reaction, and collisional stabilization.

There is increasing role of FAB mass spectrometry in other areas as well. Work by Caprioli[73] demonstrated the ability of FAB to obtain pK_a values of acids. Johnstone and Rose[74] have used FAB to examine complexation between metal cations and macrocyclic ligands in any aqueous glycerol solution. FAB mass spectrometry has been applied for the analysis of aluminium chloride-*N*-*n*-butylpyridinium chloride molten salt system which is an ionic (ion-paired) liquid formed by mixing its two solid components, aluminium chloride and *N*-*n*-butylpyridinium chloride[75]. Recently, it has been shown that FAB mass spectrometry can be an effective tool for study of the solution dynamics of complex organometallic reactions through its use in direct reaction mixture analysis. This has been successfully applied in palladium-mediated reaction of organo-mercurials with glycols[76].

Summary

Fast atom bombardment mass spectrometry is a soft ionisation technique, which is especially applicable to the analysis of high molecular weight, thermolabile and non-volatile polar or zwitterionic compounds. It has several advantages over other ionisation techniques. Biologically active molecules like vitamin B_{12}, vacomycin, boromycin, tetradotoxin and leukotriene-C_4 etc. have been successfully analyzed. Recent reports have indicated wider applications of this analytical tool in chemical and biochemical researches.

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Communications

Synthesis of AB-Ring Moiety of Sesbanimide-A†

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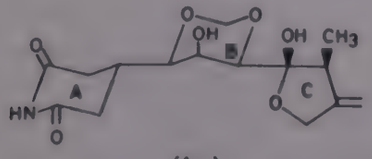
An efficient approach for the AB-ring system of sesbanimide A (**1b**), a potent anti-tumour alkaloids has been achieved from readily available D-xylose.

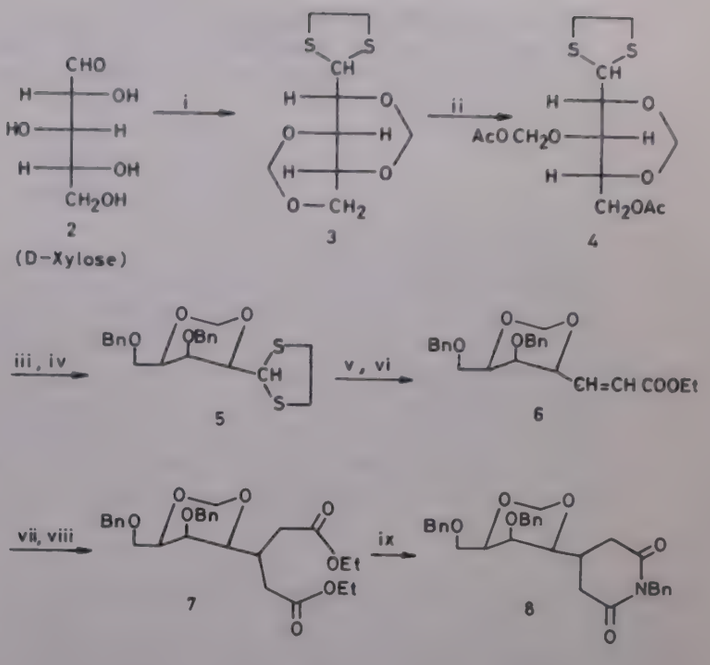
As a part of our exercise on the total synthesis of novel anti-tumour agents, we became interested in the synthesis of sesbanimide-A (**1a**) because of its potent anti-tumour activity against p 388 lymphocytic leukamia[1]. Further sesbanimide-A is a unique compound in which three rings are linked by single bonds.

Although we have completed two different approaches for the synthesis of AB-ring system of sesbanimide-A starting from D-xylose and D-glucose to give respective enantiomeric pairs, the main problem remained for want of a proper approach for the construction of ring-C. We have recently communicated[2] a simple and convenient approach for the ring-C of **1**. In view of the latest findings that the natural sesbanimide-A is an enantiomer of **1a** (**1b**) as shown by its synthesis[3], it is appropriate to report our findings for the synthesis of AB-ring system for the construction of **1b** starting from D-xylose[4].



(1a)

In our approach (Scheme 1) D-xylose was converted into the dithioacetal which on treatment with aqueous formaldehyde afforded 2,4:3,5-di-O-methylene-D-xylose-1,3-dithialane (**3**) [m.p. 210°, $(\alpha)_D + 12°$ ($CHCl_3$)] in 70% overall yield. Partial hydrolysis of the 3,5-O-methylene group in **3** was effected using a mixture of acetic anhydride-acetic acid-H_2SO_4 to give the diacetate (**4**) [m.p. 124°, $(\alpha)_D + 13°$ ($CHCl_3$)] in 76% yield. Zamplen deacetylation followed by benzylation of the resulting diol with benzyl bromide-sodium hydride furnished 3,5-dibenzylate (**5**) [m.p. 81°, (α_D)-1.5° ($CHCl_3$)] in 95% yield. Compound (**5**) on hydrolysis with mercuric perchlorate[5] in a mixture of $CHCl_3$-THF led to the aldehyde in 87% yield. Treatment of the aldehyde with ethoxycarbonylmethylenetriphenylphosphorane resulted in the formation of the α,b-unsaturated ester (**6**) (E/Z 7:3) in 82% yield. Michael reaction of **6** with diethyl malonate was conducted in the presence of sodium methoxide to afford the triester which was subjected to de-ethoxycarbonylation by heating with NaCl-water-DMSO mixture[6] to yield the syrupy diester (**7**) [$(\alpha')_D$-8.4° ($CHCl_3$)] in 70% yield. Compound (**7**) when treated with benzylamine in DMF at 170° for 3 days in a sealed tube afforded the required benzylglutarimide derivative (**8**) [$(\alpha)_D + 35°$ ($CHCl_3$)] in 87% yield.



i) Ethanedithiol, HCl, aq. HCHO
ii) Ac_2O, AcOH, H_2SO_4
iii) NaOMe, MeOH, $CHCl_3$
iv) BnBr–NaH
v) $Hg(ClO_4)_2 \cdot 3H_2O$
vi) Ph_3P=CHCOOEt
vii) $\overset{\oplus}{N}a\overset{\ominus}{C}H(COOEt)_2$
viii) DMSO–NaCl–H_2O
ix) $C_6H_5CH_2NH_2$–DMF

Scheme 1

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Nitrogen Insertion in Isolongifolane/Longibornane Systems via Beckmann/Schmidt Rearrangements: A Comparative Study†

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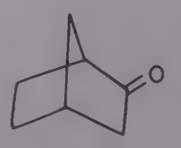
Novel nitrogen inserted compounds are formed when the 7H-epimeric 8-oxoisolongifolanes(**5**/**6**) and longibornane-4-one(**7**) are subjected to Beckmann/Schmidt rearrangements. While treatment of oxime **8** of 7αH-ketone(**5**) with tosyl chloride in pyridine gives the usual lactam(**11**) (50%) by migration of methine, oxime(**9**) of 7βH-ketone(**6**) under similar conditions generates the unusual lactam(**12**) by methylene migration. Refluxing **5** with hydroxylamine-O-sulphonic acid in acetic acid also results in **11** (13%) in a Beckmann-like rearrangement while **6** fails to react under these conditions. When exposed to sodium azide + conc. sulphuric acid in chloroform (Schmidt reaction), **5** is transformed into **11** (32%) while **6** is recovered unchanged. The Beckmann rearrangement (tosyl chloride in pyridine) of oxime (**10**) derived from **7** affords a single lactam (30%) either **14** or **15** while refluxing **7** with hydroxylamine-O-sulphonic acid in acetic acid gives a mixture of the two lactams (**14** + **15**) (16%). The tetrazole **16**/**17** (42%) is formed when **7** is subjected to Schmidt reaction with excess of hydrazoic acid.

As a part of our study dealing with electron-deficient skelatal rearrangements in longifolene chemistry[1], we have earlier described synthetically useful carbon insertions[2] via diazomethane[2a]/Arndt-Eistert[2b] reactions. In this paper the results obtained during nitrogen insertion studies in the isolongifolane/longibornane systems via Beckmann[3]/Schmidt[4] rearrangements are elaborated.

In the case of alicyclic ketoximes/ketones, the Beckmann/Schmidt rearrangements generally afford ring-enlarged lactams, the nitrogen insertion taking place on the more substituted[5] side of the ring. A fragmentation reaction generating olefinic nitriles has been occassionally observed in an abnormal[6] Beckmann while in the case of Schmidt rearrangement, tetrazoles[4b]/ureas[7] (which are otherwise inaccessible and some of which exhibit high biological activity) are formed when excess of hydrazoic acid is used in the reaction. Although both these reactions have been quite extensively studied, not many examples of bridged bicyclic/tricyclic substrates are available in the literature. One interesting example which has been subjected to both Beckmann/Schmidt reactions is that of norcamphor[8](**1**). In a Beckmann reaction, its oxime(**2**) afforded the usual lactam(**3**) while Schmidt reaction on **1** yielded the unusual lactam(**4**) arising from methylene migration instead of the expected bridge head methine migration.

In view of the above account, we selected three readily accessible bridged tricyclic ketones from longifolene chemistry for nitrogen insertion studies: the 7H-epimeric pair[9] of 8-oxoisolongifolanes(**5** **6**) and longibornane-4-one[10] (**7**). The oximes were prepared by refluxing an ethanolic solution of the ketone with hydroxylamine hydrochloride and pyridine. While the ketoximes(**8**/**9**) based on isolongifolane skeleton were single isomers, the ketoxime(**10**) of **7** was a *syn*/*anti* mixture (PMR).



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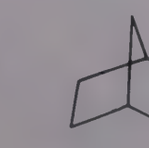
2 : R = NOH



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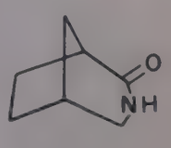

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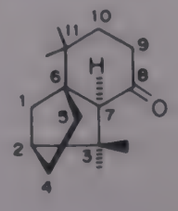

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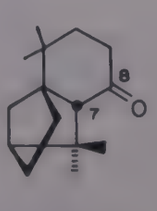

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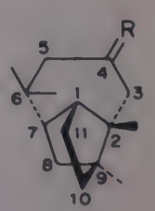
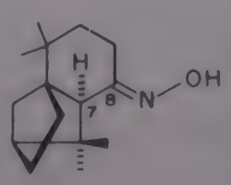


7 : R = O

10 : R = NOH



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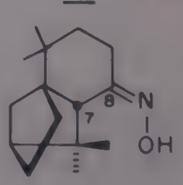
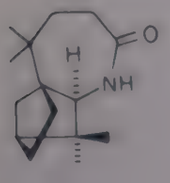


9

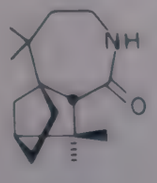
†NCL Communication No. 3927.

The tosylate esters of oximes are known to undergo Beckmann rearrangement[11] in neutral/aqueous alkaline medium under mild conditions. Thus when the 7αH-ketoxime(**8**) was treated with tosyl chloride in pyridine at ambient temperature, it afforded a crystalline compound, which on the basis of its spectral data, was assigned the usual lactam structure(**11**) arising from methine migration. Under similar conditions, its epimer **9** also generated an isomeric lactam(**12**) arising from unusual methylene migration. This was borne out by the diagnostic α-proton resonances in the PMR spectra of **11** and **12** : a 1H doublet at δ 3.34 assignable to *H*C-NH in **11** and two 1H multiplets at δ 3.10 and 3.70 due to CH_2-CH_2-NH in **12**. If one invokes the *anti*-migration rule[12] which generally operates in the Beckmann rearrangement, it means that oximes **8**,**9** have opposite configurations dictated by the C_7-H stereochemistry in the parent ketones **5**/**6**.

In a comparative study, when the Schmidt reaction was carried out by exposing the 7αH-ketone(**5**) in chloroform to hydrazoic acid generated *in situ* (sodium azide + conc. sulphuric acid) at room temperature, a crystalline compound was obtained which could be readily identified as **11**: under similar reaction conditions epimer **6** failed to undergo any reaction and was recovered unchanged. This marked difference in behaviour of the two epimeric **5**/**6** was also reflected in a Beckmann-like rearrangement performed by refluxing the substrate with hydroxylamine-O-sulphonic acid[13] in acetic acid: while **5** generated **11** (13%), **6** remained essentially unchanged. This steric constraint for attack by nucleophile in the case of **6** was also borne out by its total inertness to *m*-chloroperbenzoic acid ($CHCl_3$ solution/room temperature) while its epimer **5** underwent facile oxygen insertion generating lactone[14](**13**) under similar conditions.



11



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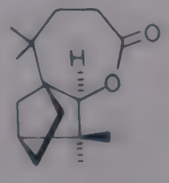

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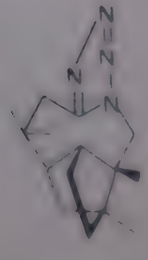
14

15



17

Despite the fact that synthesis of tetrazoles by Schmidt reaction has found wide applications, systematic studies have not been made in this field. It is not clear how the structure of the ketone affects its capacity for conversion into a tetrazole, although such a relation undoubtedly exists. Longibornane-4-one(**7**) constitutes a fine example which highlights product divergence during nitrogen insertion in ketones via Beckmann/Schmidt rearrangements. Thus when oxime(**10**) of ketone(**7**) was exposed to tosyl chloride in pyridine at room temperature, a single crystalline compound was formed which could only be assigned an either/or lactam structure(**14**/**15**) since its spectral data failed to distinguish between the two; in the Beckmann-like rearrangement carried out as before, however, the ketone **7** gave a mixture of **14** + **15** (PMR). On the other hand, while reaction of **7** in chloroform with an equimolar amount of sodium azide in conc. sulphuric acid resulted in the recovery of only starting material, treatment with excess of azide (2 mol) readily furnished a crystalline tetrazole(**16**/**17**) the formation of which can be mechanistically rationalized as shown in Scheme 1 (giving **16**).

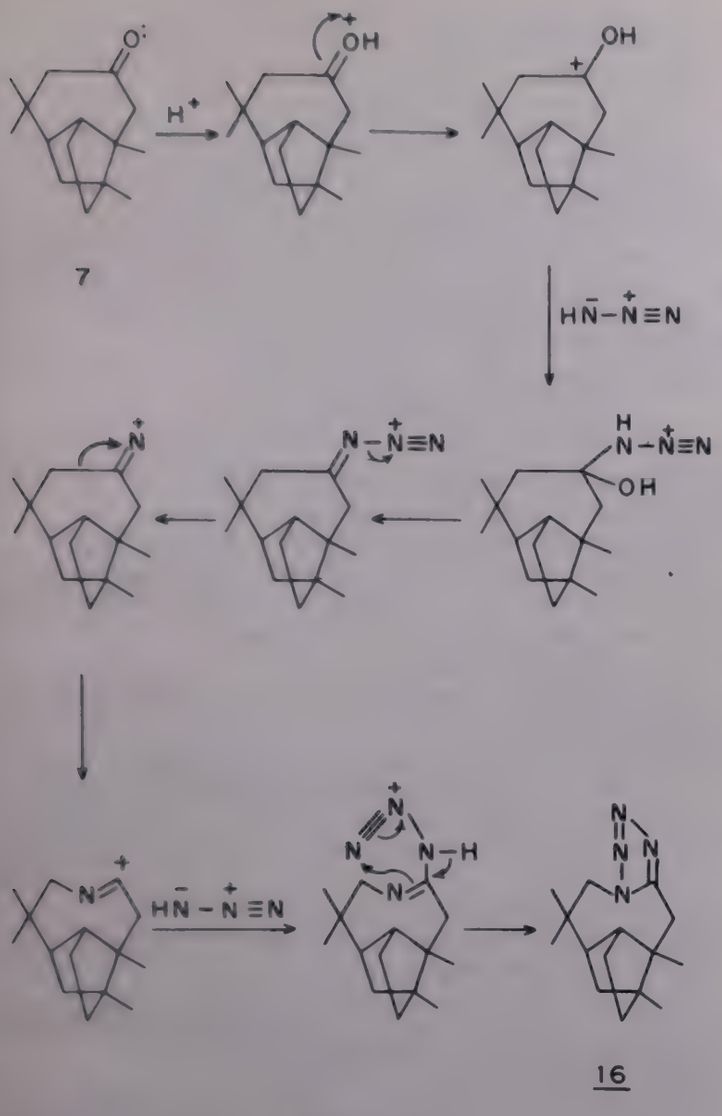
Experimental Procedure

Melting and boiling points are uncorrected. Light petroleum refers to the fraction b.p.60-80°. Freshly purified[15] and recrystallised tosyl chloride was used. Solvent extracts were dried over anhydrous Na_2SO_4. Melting points were taken in capillaries on an electrothermal melting point apparatus. IR spectra (ν_{max} in cm^{-1}) were recorded as smears (liquids) or as nujol mulls (solids) on a Pye-Unicam SP-3 IR spectrophotometer. PMR spectra were obtained on Varian T-60/FT-80A/Brucker WH-90 spectrometers and mass spectra (MS) on a CEC spectrometer model 21-110B using an ionizing voltage of 70 eV and a direct inlet system.

7αH-8-oxoisolongifolane(**5**) was prepared by the method reported by Nayak[16]. Ketone (**5**) was epimerized[9b] by refluxing in MeOH with NaOMe to give 7βH-8-Oxoisolongifolane(**6**). 4-Oxolongibornane(**7**) was prepared by 'hydration' of longifolene as reported[10] earlier.

Oximation of **5**,**6** *and* **7** : *Formation of oximes*(**8**),(**9**) *and* (**10**)

A mixture of the ketone (4.4 g), $NH_2OH.HCl$ (1.68 g), EtOH (40 ml) and pyridine (1 ml) was refluxed on a water-bath for 5 hr. The mixture was poured into ice-water, extracted with ethyl acetate (3 × 50 ml), washed



SCHEME 1

with brine, dried, solvent removed and the crude solid was recrystallized from MeOH.

7αH-8-Oximino-isolongifolane(**8**): Colourless crystals, m.p.150° (1.1 g, 24%); IR (nujol): 3340, 1660, 930; PMR (CCl_4): δ 1.15, 1.06 × 2, 0.95 (four tertiary Me singlets) (Found: C, 75.6; H, 10.8; N, 6.7. $C_{15}H_{25}ON$ requires C, 76.5; H, 10.7; N, 6.0%).

7βH-8-Oximino-isolongifolane(**9**): Colourless crystals, m.p. 188° (1.1 g, 24%); IR (nujol): 3260, 1660 (weak), 940; PMR ($CDCl_3$): δ 1.26, 0.96, 0.86, 0.83 (four tertiary Me singlets) (Found: C, 76.3; H, 10.7; N, 5.4. $C_{15}H_{25}ON$ requires C, 76.5; H, 10.7; N, 6.0%).

4-Oximino-longibornane(**9**): Colourless crystals m.p. 155-58° (3.8 g, 77%); IR (nujol): 3280, 1590. PMR (CCl_4): Methyl region between δ 0.83 and 1.00 was complex and poorly resolved indicating mixture of *syn/anti* isomers. (Found: C, 77.2; H, 10.7; N, 6.2. $C_{15}H_{25}ON$ requires C, 76.5; H, 10.7; N, 6.0%).

Action of tosyl chloride-pyridine on **8**, **9** *and* **10**: *Formation of lactams*(**11**),(**12**) *and* (**14**/**15**)

A mixture of the oxime (1 g), dry pyridine (10 ml) and tosyl chloride (1.5 g) was kept at room temperature overnight. It was acidified with 1:1 HCl (100 ml), extracted with ethyl acetate, washed with Na_2CO_3, brine, dried, solvent removed and the crude solid recrystallised from MeOH.

7αH-Lactam(**11**): Colourless crystals, m.p. 124° (0.5 g, 50%); IR (nujol): 3340, 1665, 755; PMR (CCl_4): δ 5.44 (*bs*, 1H, O=C-NH), 3.40 (*d*, 1H, C*H*-NH, J = 5 Hz), 2.4 (*m*, 2H, CH_2-CONH), 1.12 × 2, 1.00 × 2 (four tertiary Me singlets); MS: *m/z* 235 (M^+), (Found: C, 75.8; H, 10.6; N, 5.8. $C_{15}H_{25}ON$ requires C, 76.5; H, 10.7; N, 6.0%).

7βH-Lactam(**12**): Colourless crystals, m.p. 197° (0.48 g, 48%). IR (nujol): 3300, 3200, 3060, 1645, 1175. 845; PMR($CDCl_3$): δ 5.95 (*bs*, 1H, O=C−NH). 3.70 (*m*, 1H, one H of CH_2−NH−C=O), 3.10 (*m*, 1H other H of CH_2-NH-C=O), 1.25, 1.11 × 2, 0.97 (four tertiary Me singlets); MS:*m/z* 235 (M^+) (Found: C, 76.6; H, 10.7; N, 5.6. $C_{15}H_{25}ON$ requires C, 76.5; H, 10.7; N, 6.0%).

Lactam(**14**/**15**): Colourless crystals, m.p. 177-80° (0.2 g, 30%); IR (nujol): 3240, 3100, 1660; PMR ($CDCl_3$): δ 6.48 (*bs*, CONH), 3.34 (*dd*, 2H, CH_2−NHCO, $J_1 = J_2$ = 8 Hz), 2.48 (*m*, 2H, CH_2-CONH), 1.08, 1.02, 0.90, 0.72 (four tertiary Me singlets) (Found: C, 77.5; H, 10.9; N, 5.8. $C_{15}H_{25}ON$ requires C, 76.5; H, 10.7; N, 6.0%).

Action of NH_2OSO_3H *on* **5** *and* **7**: *Formation of lactams* **11** *and* **14** + **15**

A mixture of the ketone (1 g) in gl AcOH (25 ml) and NH_2OSO_3H (1 g) was refluxed for 7 hr. The mixture was diluted with water, extracted with $CHCl_3$ (3 × 50 ml), washed with 10% aq. $NaHCO_3$, brine, dried and solvent removed. The crude product in the case of **5** (TLC: 2 spots) was separated by chromatography on a column of silica gel (TLC monitoring): Fr. 1, light petroleum-benzene (1:1), 2 × 50 ml, unchanged **5** (0.06 g). Fr. 2, 10% EtOAc in benzene, 4 × 50 ml, pure solid; this was recrystallized from light petroleum to give the lactam(**11**) (0.15 g, 13%), identified by m.p., IR/PMR.

In the case of **7**, the crude product was a solid which was directly recrystallized from light petroleum to furnish colourless crystals, m.p. 127-32°; IR (nujol): 3220, 1660. PMR ($CDCl_3$): atleast 8 signals in the methyl region between δ0.74 and 1.10; possibly a mixture of isomeric lactams **14** + **15**.

Schmidt reaction on 7αH-8-oxoisolongifolane (**5**): *Formation of lactam* (**11**)

A stirred mixture containing **5** (2.2 g, 10 mmol) in $CHCl_3$ (20 ml) and conc. H_2SO_4 (8 ml) was cooled in an ice-bath and treated with NaN_3 (1.62 g, 25 mmol) in portions during 30 min. After stirring for 15 min more, the mixture was diluted with ice water, basified with dil KOH solution, extracted with ether, washed with

brine, dried, solvent removed and the mixture chromatographed on silica gel/IIa column (with TLC monitoring): Fr. 1, benzene, 5 × 25 ml, ketone(**5**) (0.1 g). Fr. 2, 5% EtOAc in benzene, 4 × 25 ml, mixture (0.41 g). Fr. 3, EtOAc, 6 × 25 ml, pure lactam(**11**) (0.8 g, 32%), identified by m.p., IR/PMR.

Schmidt reaction on longibornane-4-one(**7**):

Formation of tetrazole(**16**/**17**)

A stirred mixture containing **7** (2.2 g) in $CHCl_3$ (20 ml) and conc. H_2SO_4 (8 ml) was subjected to Schmidt reaction with NaN_3 (1.62 g, 25 mmol) as described for **5**. In this case the crude product was a solid which was recrystallised from light petroleum to afford the tetrazole(**16**) or (**17**) as colourless needles, m.p. 155-57° (1.1 g; 42%); IR(nujol): 1535, 1100, 1080, 1000, 790. PMR (CCl_4): δ 4.01 (*d*, 2H, H_2C-N, J = 5 Hz), 2.65 (*s* 2H, $H_2C-C=N-$), 1.05 × 2, 0.96 × 2 (four tertiary Me singlets); MS: *m/z* 260 (M^+, base peak) (Found: C, 69.2; H, 9.2; N, 20.7. $C_{15}H_{24}N_4$ requires C, 69.2; H, 9.2; N, 21.5%).

Action of m-chloroperbenzoic acid on epimeric ketones(**5**) *and* (**6**)

A mixture containing **5**/**6** (0.22 g) in $CHCl_3$ (5 ml) and *m*-chloroperbenzoic acid (0.21 g) was stirred at room temperature overnight. The mixture was diluted with $CHCl_3$ (20 ml), washed with 2% aq. KOH, brine, dried and solvent removed. In the case of **5** the crude semi-solid was recrystallised from light petroleum to furnish the lactone(**13**) (25 mg), identified by m.p., IR/PMR.

In the case of **6** there was no reaction at all and the entire material was recovered unchanged (identified by IR/PMR).

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Silver Ion-Assisted Solvolysis of 8,11-Dibromolongibornane: Generation of Novel Skeletally Rearranged Olefinic Carbinols†

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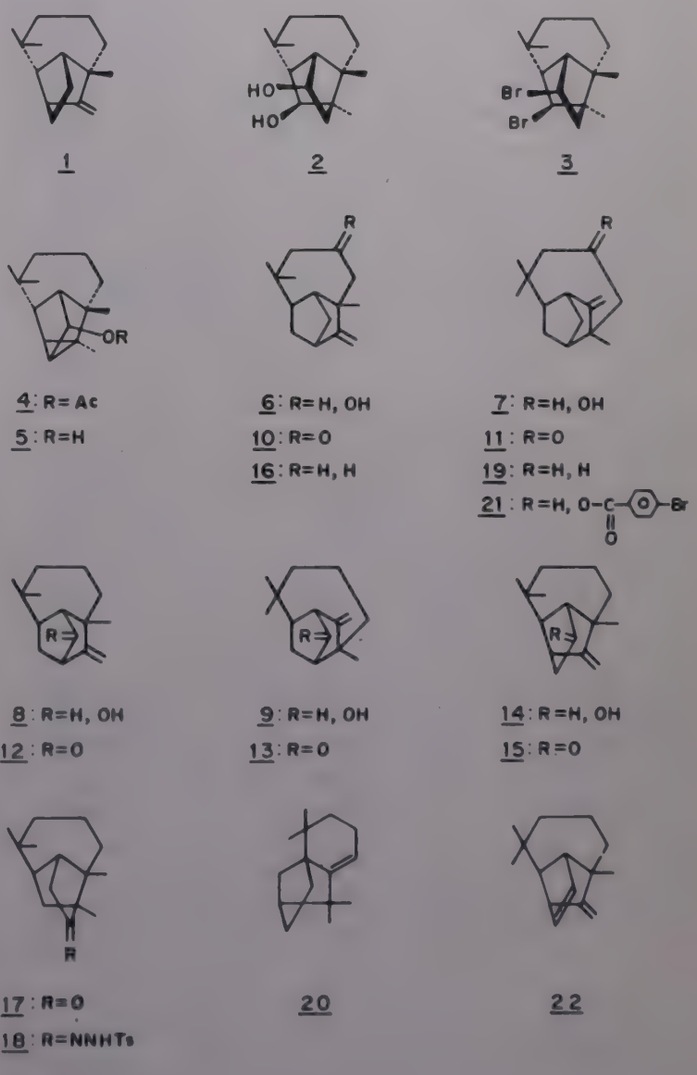
The disecondary bromide, 8, 11-dibromolongibornane (**3**) on exposure to silver perchlorate in aqueous acetone gives predominantly a mixture of three olefinic carbinols, of which a unique ring-expanded alcohol (**7**) constitutes 65%; the assigned structure has been confirmed by an X-ray analysis of its *p*-bromobenzoate. Of the other two minor alcohols (separable only in the form of their ketones), one has been characterized as 10-ketolongifolene (**15**); the other keto-olefin which is highly hindered and resistant to Wolff-Kishner reduction has been assigned one of two possible structures **12**/**13** based on spectral data. The minor hydrocarbon fraction (6%) has been shown to consist of two compounds of which only one has been characterized as dehydrolongifolene (**22**).

As part of our efforts aimed at conversion of longifolene (**1**) into other naturally occurring sesquiterpenoids, we have recently described[1] its transformation into culmorin (**2**)—a sesquiterpene diol mould metabolite of *Fusarium culmorum*. After considerable experimentation in the synthetic strategy, a viable intermediate, viz. 8, 11-dibromolongibornane (**3**) finally became available; a bis-solvolysis of **3** was theoretically expected to give **2** but in actual practice this transformation could not be achieved. We now describe, in detail, the silver ion-assisted solvolysis of **3** which was resulted in the isolation of skeletally rearranged olefinic carbinols and olefinic ketones (after Jones' oxidation); of these 10-ketolongifolene (**15**) has been exploited for the synthesis of **2** as reported[1] earlier.

In a simplified method for preparation of **3**, 11-acetoxylongicyclene (**4**) (resulting from action[2] of acetic acid—50% aq. sulphuric acid on dehydrolongifolene) was directly exposed to hydrogen bromide in acetic acid at ambient temperature; this reaction was earlier[1] performed on the alcohol (**5**) obtained after hydrolysis of the initially formed **4**.

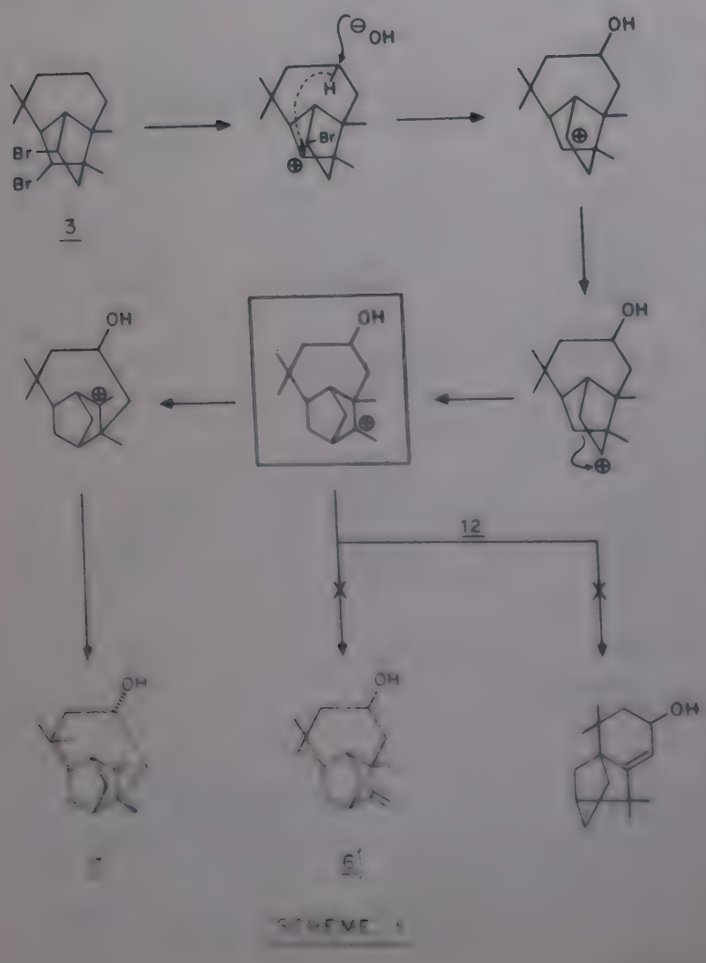
Of the several applications[3] of silver perchlorate in synethetic transformations, its use as a reagent for achieving solvolysis, rearrangement[4] and valence isomerization deserves special mention. Thus, Reese and coworkers[5] have recently used silver perchlorate in aqueous acetone for solvolysis of halocyclopropanes. The superiority of silver perchlorate (in 50% aq. acetone) over other common reagents in the hydrolysis of secondary bromide intermediates for synthesis of 11-hydroxyprostanoids[6] prompted us to apply this reagent and study its scope as a solvolytic reagent for mono- and di-secondary halides based on bridged tricyclic systems derived from longifolene (**1**). Exposure of the disecondary bromide bromide, i.e. **3** to silver perchlorate in 50% aq. acetone at ambient temperature overnight, led to a complex mixture,



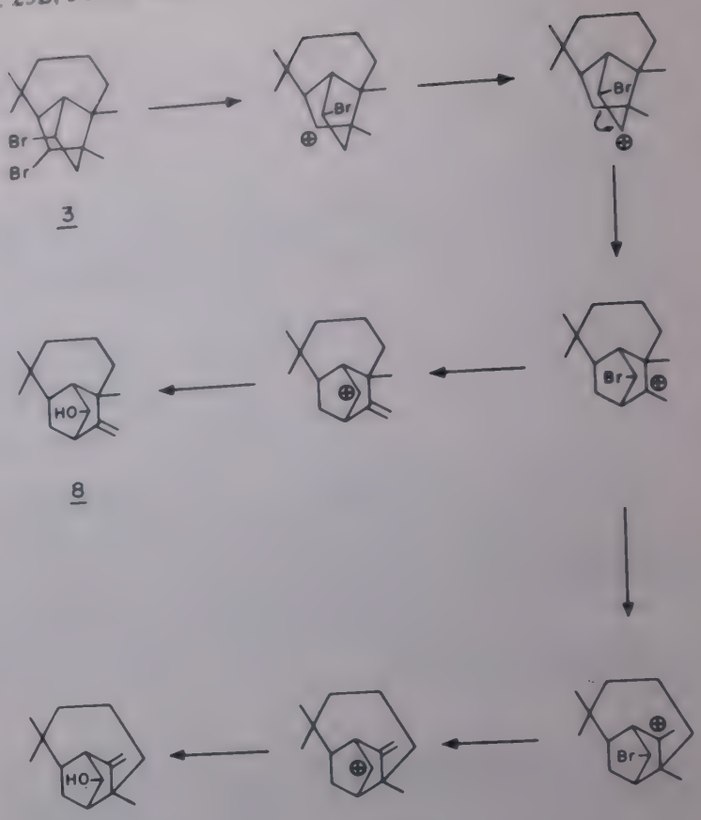
†NCL Communication No. 3952.

which on column chromatography over silica gel, predominantly gave three olefinic secondary alcohols (94%) preceded by a negligible amount (6%) of olefins but without evidence of any diol. One of these carbinols **7**, having a unique ring-expanded carbon skeleton (*vide infra*) constituted about 65% of the mixture and was readily separated pure as a crystalline solid (m.p. 98°) while the other two remained as a mixture; they could, however, be resolved in the form of pure ketones, after Jones' oxidation of the mixture, followed by chromatography.

The spectral data (*vide* Experimental) of **7** clearly indicated it to be an *exo*-methylenic secondary alcohol. Oxidation of **7** with Jones' reagent followed by Wolff-Kishner reduction of the resulting keto-olefin resulted in an *exo*-methylenic hydrocarbon whose spectral characteristics (IR/PMR) were distinctly different from those of **1**. Thus it was clear that parent **7** had a non-longifolene type of skeleton. On mechanistic grounds (see Schemes 1 and 2), four structures **10** to **13** (respectively derived from olefinic carbinols **6** to **9**) came up for consideration for the keto-olefin. The IR frequency of the carbonyl group in the keto-olefin being in the normal region at 1700 cm^{-1}, structures **12**/**13** which incorporate a cyclopentanone, could be eliminated (absence of peak around 1750 cm^{-1}). Furthermore, the deoxo compound mentioned earlier was also found to be different (IR/PMR) from



SCHEME 1



SCHEME 2

neolongifolene[7] (**16**) [formed when the tosylhydrazone (**18**) of longicamphor (**17**) was refluxed with sodium in ethylene glycol in a protic Bamford-Stevens reaction] and can therefore be represented by the remaining *pseudo*-neolongifolene (**19**) whose skeleton is unprecedented in longifolene chemistry; a structure of this type was envisaged to collapse into isolongifolene (**20**) in the presence of acid following the now well-established Berson[8] mechanistic pathway and this indeed proved to be so when exposure of **19** to BF_3-etherate in benzene at room temperature smoothly transformed it into **20**. From the foregoing, it is clear that the keto-olefin should be **11** and the parent olefinic carbinol, **7**. It now appeared also desirable to confirm the assigned structure **7** by an X-ray study. For this purpose the crystalline *p*-bromobenzoate derivative proved to be highly satisfactory and its X-ray‡ analysis dictated structure **21** for the compound thus vindicating the earlier assigned structure **7** for the parent alcohol.

In an attempt to assign structures to the pair of keto-olefins (separated by chromatography after oxidation of the two minor olefinic carbinols formed in the solvolysis of **3**) mentioned earlier, both were subjected

‡X-ray diffraction analysis of the *p*-bromobenzoate was carried by T N Guru Row and coworkers of this laboratory. A detailed discussion on the crystal and molecular structure of the compound will appear elsewhere

to Wolff-Kishner reduction. One of them readily gave longifolene (**1**) as the deoxo compound and hence its progenitor was given the 10-keto-longifolene structure **15** (formed *via* alcohol **14**); the validity of this assignment was further proved by its conversion into culmorin (**2**) as reported[1] earlier. The other keto-olefin, however, failed to give the deoxo compound under a variety of modified[9] Wolff-Kishner reduction conditions and was recovered essentially unchanged. The highly hindered nature of the carbonyl group in this compound which was responsible for its resistance to reduction makes either of the structures **12/13** (and hence structures **8/9** for the parent olefinic carbinols) attractive but further differentiation was not possible from spectral data (IR/PMR).

The minor hydrocarbon fraction (6%) formed in the solvolysis of **3** was also investigated by chromatography over silver nitrate-impregnated silica gel when two pure olefins were separated. While the slower-moving one was readily characterized as the known dehydrolongifolene[2] (**22**) (IR/PMR), the other hydrocarbon (also $C_{15}H_{22}$, M^+ 202) was obviously based on a new tetracyclic skeleton bearing one vinylidene group; a definite structure assignment, however, could not be made due to paucity of material.

Experimental Procedure

All m.ps and b.ps are uncorrected. Light petroleum refers to the fraction b.p. 60-80°. Solvent extracts were dried over anhydrous Na_2SO_4. Silver perchlorate was freshly prepared[10] and dried[11]. IR spectra (ν_{max} in cm^{-1}) were recorded as smear (liquid) or nujol mull (solid) on a Pye-Unicam SP-3 IR spectrophotometer. PMR spectra were taken on a Varian T60/FT-80A/Bruker WH-90 spectrometers and mass spectra (MS) on a CEC spectrometer model 21-110B, using an ionizing voltage of 70 eV and a direct inlet system. The X-ray data for **21** were collected on a Enraf-Nonius CAD4-11M diffractometer. 11-Acetoxylongicyclene (**4**) was prepared by the action of acetic acid-50% aq. H_2SO_4 on dehydrolongifolene (**22**) as reported[2].

Action of HBr-AcOH on 11-*acetoxylongicyclene*. (**4**): *Formation of* 8,11-*dibromolongibornane* (**3**)

A mixture of **4** (15 g) and 32% HBr-AcOH (100 ml) was kept at room temp. (18 hr). The separated crystalline dibromide (**3**) was filtered and recrystallised from ethanol. The mother liquor was diluted with water (100 ml), extracted with ether, washed with 5% aq. $NaHCO_3$, brine, dried, solvent removed and the crude product chromatographed on silica gel/IIa (100 g). Elution with light petroleum gave some more crystalline **3**; m.p. 124° (EtOH) (total yield 16.5 g, 79%); identified[1] by IR/PMR.

Solvolysis of 8,11-*dibromolongibornane* (**3**)

To a solution of **3** (16 g) in 50% aq. acetone (300 ml), $AgClO_4$ (18 g) was added and stirred at room temp. (18 hr). The reaction mixture was filtered, filtrate diluted with water (300 ml), extracted with EtOAc (3 × 100 ml), washed with brine, dried and solvent removed. The crude product (10 g) was chromatographed on silica gel/IIa (360, 160 cm × 10 cm) with TLC monitoring; Fr. 1, light petroleum, 4 × 100 ml, mixture. Fr. 2, benzene, 6 × 100 ml, pure solid. Fr. 3, 1% EtOAc in benzene, 8 × 100 ml mixture.

Fr. 2, was recrystallized from light petroleum to furnish 4-hydroxy-pseudoneolongifolene (**7**) as colourless needles m.p. 98° (6.2 g, 65%); IR (nujol): 3300, 3080, 1660, 875. PMR (CCl_4): δ 0.96, 1.01, 1.06 (*s*, 3H, three tertiary methyl singlets), 4.25 (br *m*, C-4-C*H*-OH), 4.58 and 4.78 (two *s*, 1H each, $\gtrsim C=CH_2$); MS: *m/z* 220 (M^+) (Found: C, 82.7; H, 10.7. $C_{15}H_{24}O$ requires C, 81.8; H, 10.9%).

Fr. 1, mixture (0.4 g) was rechromatographed on 15% $AgNO_3$ impregnated silica gel[12] (20 g) with TLC-monitoring: Fr. 1a, light petroleum, 4 × 50 ml, pure. Fr. 1b, light petroleum, 3 × 50 ml, pure, b.p. 100°/0.5 mm (0.2 g, 4%) (identified[2] as dehydrolongifolene (**22**) by IR/PMR.

Fr. 1a, tetracyclic olefin, colourless liquid, b.p. 100°/0.5 mm (0.18 g, 2%); IR (smear): 3100, 1639, 890; PMR ($CDCl_3$): δ 0.88, 1.04, 1.08 (*s*, 3H, three tertiary methyl singlets), 4.76 and 4.96 (two *s*, 1H each, $>C=CH_2$); CMR ($CDCl_3$): 160,71 (*s*, 102.8 (*t*) ppm; MS: *m/z* 202 (M^+, base peak) (Found: C, 88.6; H, 11.1. $C_{15}H_{22}$ requires C, 89.0; H, 10.9%). Fr. 3, (3.6 g) was oxidised with Jones' reagent and the mixture of keto-olefins (3.4 g) chromatographed on silica gel/IIa (160 g, 120 cm × 6.5 cm). Fr. 1, light petroleum-benzene (1:1), 6 × 100 ml, pure. Fr. 2, light petroleum-benzene (1:1), 7 × 100 ml, pure. Fr. 1, keto-olefin **8/9**, b.p. 140°/0.5 mm (0.5 g, 5%); IR (smear): 3100, 1750, 1670, 890; PMR ($CDCl_3$): δ 1.00, 1.12, 1.16 (*s*, 3H three tertiary methyl singlets), 3.16 (br, *m*, $H_2C=C-CH-C=O$), 4.88 and 5.20 (two *s*, 1H each, $>C=CH_2$); MS: *m/z* 218 (M^+, base peak). (Found: C, 81.8; H, 10.2. $C_{15}H_{22}O$ requires C, 82.5; H, 10.1%). Fr. 2, distilled at 140°/0.5 mm (2.5 g, 25%) characterized[1] as 10-ketolongifolene (**15**) by IR/PMR.

4-*Keto-pesudoneolongifolene* (**11**)

A mixture of **7** (2.2 g) in acetone (20 ml) treated with Jones' reagent (0.5 ml) and stirred at room temp. (2 hr). The mixture was diluted with water, extracted with benzene, washed with 5% aq. $NaHCO_3$, water, brine, dried and solvent removed. Distillation (b.p. 140°/0.5 mm) afforded **11** (1.8 g, 80%); IR (smear): 3080, 1700, 890; PMR ($CDCl_3$): δ 0.96, 1.00, 1.04 (*s*, 3H, three tertiary

methyl singlets), 4.84 and 5.12 (two *s*, 1H each, $>C=CH_2$); MS: *m/z* 218 (M^+, base peak) (Found: C, 81.6; H, 10.0. $C_{15}H_{22}O$ requires C, 82.5; H, 10.1%).

Wolff-Kishner reduction of 4-keto-pesudoneolongifolene (**11**): *Formation of pseudoneolongifolene* (**19**)

A mixture of **11** (0.6 g), hydrazine hydrate (85%, 12 ml), KOH (3 g) and diethylene glycol (125 ml) was refluxed for 1 hr. Water and excess hydrazine were distilled out and refluxing continued for 3 hr. The cooled reaction mixture was diluted with water (50 ml), extracted with light petroleum, washed with brine, dried, solvent removed and the crude product chromatographed on silica gel/IIa (40 g, 20 cm × 2 cm). Elution with light petroleum gave **19**, b.p. 100°/0.5 mm (bath) (1.3g, 55%); IR(smear): 3080, 3040, 1660, 880, 870; PMR ($CDCl_3$): δ 0.92, 1.00, 1.04 (three tertiary methyl singlets), 2.72 (*bm*, 1H allylic), 4.48 and 4.94 (two *s*, 1H each, $>C=CH_2$); MS: *m/z* 204 (M^+, base peak) (Found: C, 88.2; H, 11.8. $C_{15}H_{24}$ requires C, 88.2; H, 11.8%).

Action of BF_3-etherate on pesudoneolongifolene (**19**): *Formation of isolongifolene* (**20**)

To a mixture of **19** (0.2 g), in dry benzene (10 ml), freshly distilled BF_3-OEt_2 (4 drops) was added and left at room temp. (18 hr). After diluting with more benzene, the organic extract was washed with 5% aq. $NaHCO_3$, brine, dried, solvent removed and the residue distilled to obtain **20**, identified by IR/PMR.

Pesudoneolongifolyl-p-bromobenzoate (**21**)

A mixture of **7** (0.22 g), dry benzene (10 ml), freshly distilled *p*-bromobenzoyl chloride (0.24 g) and pyridine (0.1 ml) was refluxed for 4 hr. The mixture was diluted with more benzene, washed successively with dil. HCl, water, aq. $NaHCO_3$, brine, dried and solvent removed. The crude product was recrystallized from light petroleum to furnish **21** as colourless needles m.p. 216°; IR (nujol): 3100, 1790, 1725, 860, 830, 740, 690; PMR ($CDCl_3$): δ 1.0, 1.16, 1.16 (*s*, 3H, three needles; methyl singlets), 4.76, 4.96 (two *s*, 1H, $>C=CH_2$), 5.92 (*bm*, 1H, *H*C-COPhBr), 7.60 (*d*, 2H, aromatic, J = 12Hz), 7.96 (*d*, 2H, aromatic, J = 12Hz).

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Synthetic Experiments in Lignans: Part IX—Thermal & Photochemical Cyclisations of Diarylidenesuccinic Anhydrides & a Synthesis of Dehydrolintetralin

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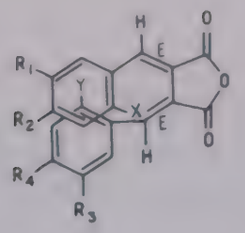
Thermal and photochemical cyclisations of some dibenzylidenesuccinic anhydrides (Ia to Ic) lead to the formation of a mixture of 1-phenylnaphthalene anhydrides. Blocking of one of the cyclisable positions in any one of the two aryl nuclei by bromine atom shows no regeospecificity in directing cyclisation into the non-halogenated aryl nucleus either during thermal or photochemical cyclisation. Cyclisation even into the halogenated aromatic nucleus itself, expected to be stereoselective, is non-stereoselective. The products are preferentially formed by elimination of HBr rather than H_2. Incidentally, the naphthalene analogue (VI) of lintetralin, a natural tetralin from *Phyllanthus niruri* and the respective partial monomethyl ethers (Vm and Vn) have been prepared and characterised by their PMR spectra.

Diarylidenesuccinic anhydrides having dissimilar aryl rings undergo cyclisation[1,2] yielding a mixture of 1-phenylnaphthalene-2,3-dicarboxy anhydrides, cyclisation being effected into both the aryl rings. Diarylidenesuccinic anhydrides, generally prepared by the two-stage Stobbe reaction from the respective aromatic aldehydes, are selectively obtained in the (*E*, *E*) configuration (I) if the starting aldehydes have either both the *ortho*-positions free or have only one *ortho* substituent[3]. But no such stereoselectivity is noticed with aromatic ketones or with aldehydes substituted in both the *ortho* positions[4-6]. Further, these diarylidenesuccinic anhydrides undergo $E \rightleftharpoons Z$ isomerisation (II$\rightleftharpoons$III) at temperatures > 180°C beofre the ring closure occurs by the allowed disrotatory electrocyclic mode. The photochemical cyclisation at room temperature may go through the allowed conrotatory mode from the (*E*, *E*) configuration of the anhydride without isomerisation leading to the same intermediates (B or C) as in thermal cyclisation. Of the thermal methods of cyclisations, heating of the diarylidenesuccinic anhydrides at reflux temperature (260°C) of diphenyl ether has been reported[7,8] to be the most effective method with more than 80% yield of the cyclised products.

Piperonylidene-veratrylidenesuccinic anhydride (Ia) was reported to give a 1:1 mixture of the two isomeric 1-phenylnaphthalene-2,3-dicarboxy anhydrides (IVa and IVb) when heated at 265-70° in the absence of a solvent[1]. The same anhydride was, however, reported to give only one isomer (IVa) with yields greater than 50% under different oxidative[9,10] and thermal[11] methods of cyclisation, thereby suggesting greater reactivity of the piperonyl ring compared to the veratryl ring. The cyclisation of the anhydride (Ia) has now been repeated under thermal and photochemical conditions.

Refluxing Ia in diphenyl ether[7,8] for 45 min resulted in the formation of 1-phenylnaphthalene anhydride in almost quantitative yield, which, although showed a single spot in TLC, was found to be a mixture (PMR). The percentage of the two anhydrides (IVa and IVb) in the mixture could be assessed as 60:40 from the intensity of the methylenedioxy signals, which appear to be diagnostic, the one at higher field (δ 6.04) could be due to IVa and the other at δ 6.12 to IVb. Separation of the mixture by column chromatography over silica gel resulted only in poor separation (only 70 mg of IVa and 25 mg of IVb). The remaining mixture (850 mg) after the separation of IVa and IVb was hydrolysed with alkali and esterified with diazomethane to yield the ester mixture which on crystallisation gave Ve (300 mg) and a 1:1 mixture (450 mg) of Ve and Vf. The anhydride (IVa) and the corresponding ester (Ve) agreed well in their physical and spectral data with those reported earlier[16]. The isomeric anhydride (IVb) and the ester (Vf) have now been fully characterised by their PMR data (see Experimental) (Chart A).

The dimethyl ester (Vf) was reduced with LAH to yield the diol (Vk) which on methylation gave the corresponding dimethyl ether (Vl) along with the partial monomethyl ethers (Vm) and (Vn). These three methyl ethers have now been described for the first time and characterised by their PMR spectra. The partial methyl ethers could be distinguished by the respective aliphatic methoxy signal, which appears at higher field (δ 3.29) in the 2-methoxymethyl compound (Vm) compared to that at δ 3.48 for the 3-

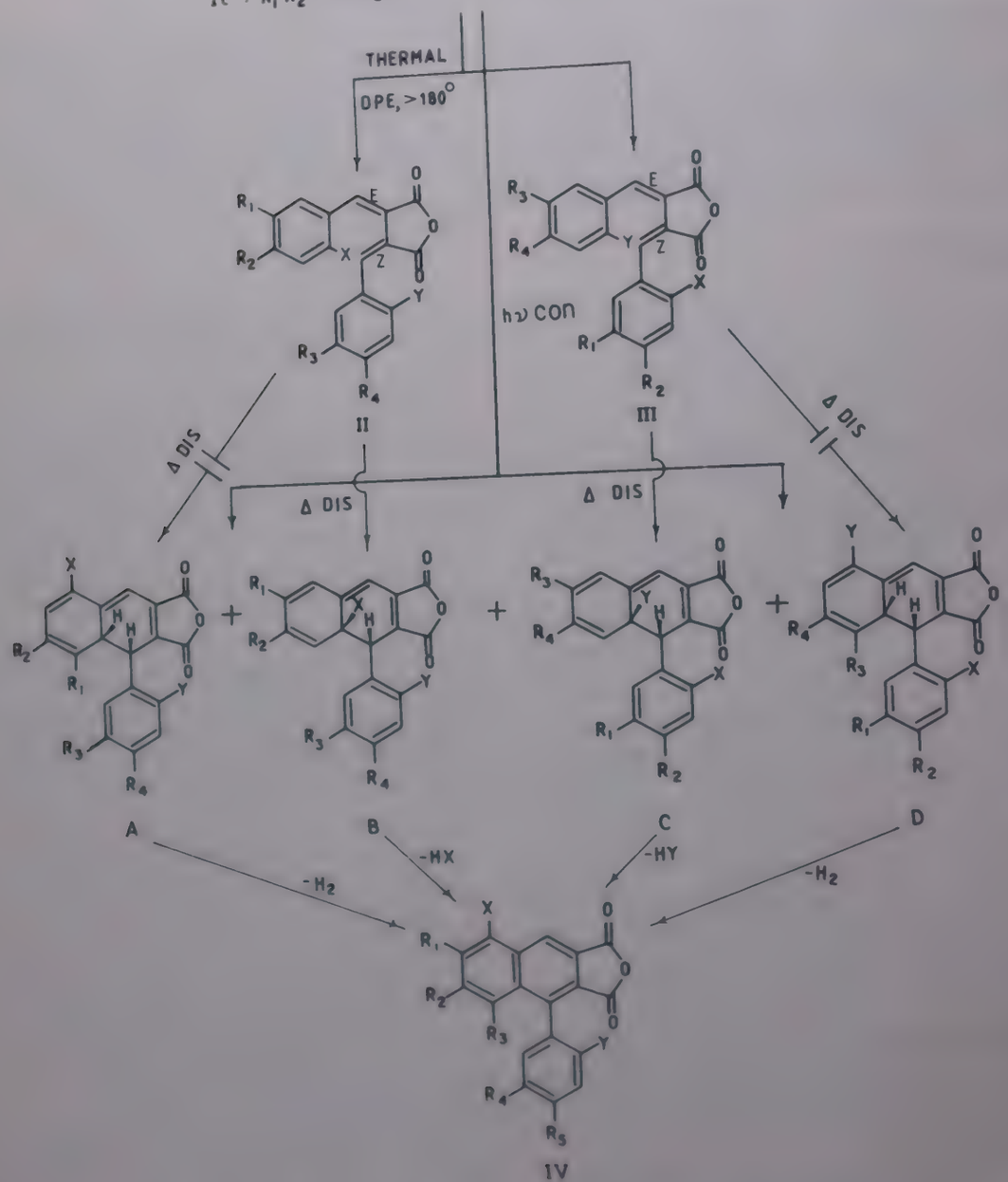


I

Ia : $R_1R_2 = -OCH_2O-$, $R_3 = R_4 = -OCH_3$, X = Y = H

Ib : $R_1R_2 = -OCH_2O-$, $R_3 = R_4 = -OCH_3$, X = Br, Y ≠ H

Ic : $R_1R_2 = -OCH_2O-$, $R_3 = R_4 = -OCH_3$, X = H, Y = Br



IV

IVa $R_1R_2 = -OCH_2O$, $R_4 = R_5 = -OCH_3$, $R_3 = X = Y = H$

IVb $R_1 = R_2 = -OCH_3$, $R_4R_5 = -OCH_2O$, $R_3 = X = Y = H$

IVc $R_1 = R_2 = -OCH_3$, $R_4R_5 = -OCH_2O$, $R_3 = X = H$, $Y = Br$

IVd $R_1R_2 = -OCH_2O$, $R_4 = R_5 = -OCH_3$, $R_3 = X = H$, $Y = Br$

IVe $R_2 = R_3 = OCH_3$, $R_4R_5 = -OCH_2O$, $R_1 = Y = H$, $X = Br$

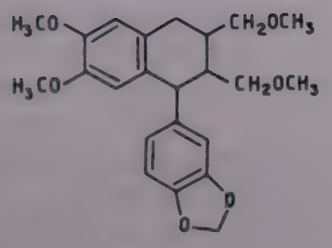
IVf $R_2R_3 = -OCH_2O$, $R_4 = R_5 = -OCH_3$, $R_1 = Y = H$, $X = Br$

CHART - A

methoxymethyl compound (Vn) due to 1-phenyl anisotropy. The dimethyl ether (Vl) might be termed as dehydrolintetralin, the naphthalene analogue of lintetralin (VI) isolated from *Phyllanthus niruri*. The DDQ treatment[14,15] of lintetralin (VI) earlier failed to give VI (Chart B).

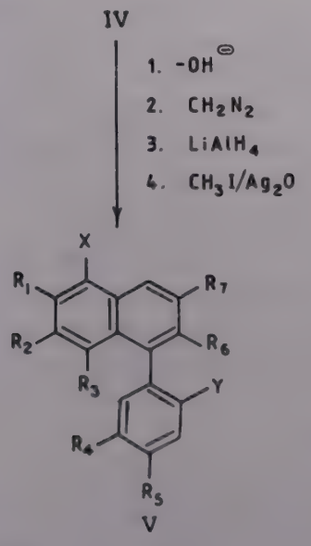
Photochemical cyclisation of the anhydride (Ia) by irradiation with medium pressure mercury lamp (>300nm) in benzene in the presence of iodine for 10 hr, resulted in the formation of a 1:1 mixture containing IVa and IVb. The vacant *para* position to the electron donating oxygen of the methylenedioxy group in a piperonyl ring or a methoxyl group in veratryl ring is very reactive for electrophilic aromatic substitution by stereo and electronic factors. We thought of blocking this position, by an halogen atom in the piperonyl in order to achieve regiospecific cyclisation into the other ring, i.e. veratryl ring. For this we prepared 6-bromopiperonylideneveratryl-idenesuccinic anhydride (Ib), and this was found by PMR to have (*E*, *E*) configuration at both the double bonds. Ib was refluxed in diphenyl ether for 1 hr when an isomeric mixture (4:6; PMR) of anhydrides (IVa and IVc) was obtained. These were readily separated by fractional crystallisation from acetone, and characterised by their PMR data.

Photochemical cyclisation of the anhydride (Ib) also resulted in a mixture of IVa and IVc (4:6; PMR) in 80% overall yield. Although veratryl substituted derivative (IVc) is obtained in higher yield, which is a positive effect of the blocking of the reactive *para*-position in the piperonyl we could not achieve regiospecificity to give exclusively IVc. Further, when the reactive *para*-position in the veratryl or piperonyl unit is blocked by bromine, the cyclisation can be expected to go regioselectively at the other vacant *ortho*-position. The product would have been (IVf) formed by elimination of H_2 by attack at the *ortho*-position, but significantly enough, it is IVa that is formed by attack at the *para*-position by eventual elimination of ·HBr. Such



VI

LINTETRALIN



V

Va :	$R_1, R_2 = -OCH_2O-$,	$R_4 = R_5 = OCH_3$,	$R_6 = R_7 =$ COOH,	$R_3 = X = Y = H$.
Vb :	$R_1 = R_2 = -OCH_3$,	$R_4 R_5 = OCH_2O$,	$R_6 = R_7 =$ COOH,	$R_3 = X = Y = H$
Vc :	$R_1 = R_2 = -OCH_3$,	$R_4 R_5 = OCH_2O$,	$R_6 = R_7 =$ COOH,	$R_3 = X = H$, $Y = Br$
Vd :	$R_1 R_2 = -OCH_2O$,	$R_4 = R_5 = OCH_3$,	$R_6 = R_7 =$ COOH,	$R_3 = X = H$, $Y = Br$
Ve :	$R_1 R_2 = OCH_2O$,	$R_4 = R_5 = OCH_3$,	$R_6 = R_7 = COOCH_3$,	$R_3 = X = Y = H$
Vf :	$R_1 = R_2 = OCH_3$,	$R_4 R_5 = OCH_2O$,	$R_6 = R_7 = COOCH_3$,	$R_3 = X = Y = H$
Vg :	$R_1 = R_2 = OCH_3$,	$R_4 R_5 = OCH_2O$,	$R_6 = R_7 = COOCH_3$,	$R_3 = X = H$, $Y = Br$
Vh :	$R_1 R_2 = OCH_2O$,	$R_4 = R_5 = OCH_3$,	$R_6 = R_7 = COOCH_3$,	$R_3 = X = H$, $Y = Br$
Vi :	$R_2 = R_3 = OCH_3$,	$R_4 R_5 = OCH_2O$,	$R_6 = R_7 = COOCH_3$,	$R_1 = Y = H$, $X = Br$
Vj :	$R_1 R_2 = OCH_2O$,	$R_4 = R_5 = OCH_3$,	$R_6 = R_7 = CH_2OH$,	$R_3 = X = Y = H$
Vk :	$R_1 = R_2 = OCH_3$,	$R_4 R_5 = OCH_2O$,	$R_6 = R_7 = CH_2OH$,	$R_3 = X = Y = H$
Vl :	$R_1 = R_2 = OCH_3$,	$R_4 R_5 = OCH_2O$,	$R_6 = R_7 = CH_2OCH_3$,	$R_3 = X = Y = H$
Vm :	$R_1 = R_2 = OCH_3$,	$R_4 R_5 = OCH_2O$,	$R_6 = CH_2OCH_3$, $R_7 = CH_2OH$,	$R_3 = X = Y = H$
Vn :	$R_1 = R_2 = OCH_3$,	$R_4 R_5 = OCH_2O$,	$R_6 = CH_2OH$, $R_7 = CH_2OCH_3$,	$R_3 = X = Y = H$

CHART - B

observation was noticed earlier in our laboratories[13], only in examples where both the aryl rings were substituted by bromine atoms in their respective *ortho* positions.

Piperonylidene-6-bromoveratrylidenesuccinic anhydride (Ic), having (*E*, *E*) configuration (PMR) was prepared next with a view to seeing the effect of blocking of the *para*-position of the veratryl ring. Ic when refluxed in diphenyl ether yielded a mixture (6:4) of the naphthalene anhydrides (IVd and IVb) in overall 90% yield. The mixture was separated by fractional crystallisation from acetone. In the case of Ic also the cyclisation showed no regiospecificity although it was effected relatively more into the piperonyl nucleus with no bromine atom. The effect of introduction of bromine into veratryl unit is not, however, comparable as the cyclisation of Ia with no bromine in the veratryl ring, also occurred into the piperonyl nucleus to the same extent.

Photochemical cyclisation of Ic gave the linearly cyclised anhydride mixture (IVd and IVb) in 75% yield, besides the angularly cyclised product, 1-(3',4'-methylenedioxyphenyl)-5-bromo-7,8-dimethoxynaphthalene-2,3-dicarboxy anhydride (IVe) in minor amount. It is significant to note that this product was not formed even in traces during thermal cyclisation. The naphthalene anhydride (IVe) was characterised by its PMR spectrum. It was also converted into the corresponding ester (Vi). The formation of two or more of the possible four naphthalene derivatives (linear and angular) during photochemical cyclisation only and that of only two linear derivatives during thermal cyclisation has been noticed by us earlier also.

Experimental Procedure

All the melting points reported are uncorrected. Unless otherwise stated, IR spectra (ν_{max} in cm^{-1}) were recorded in KBr on a Shimadzu-IR-408 spectrophotometer. PMR spectra on Perkin-Elmer 90 MHz NMR instrument (Chemical shifts are expressed in δ-scale downfield from TMS) and UV spectra on a Shimadzu-UV-140. Column chromatography was performed using silica gel (100-200 mesh, Acme).

General procedure for Stobbe condensation

A solution of aromatic aldehyde (0.05 mol) and diethyl succinate (0.06 mol) or a solution diethyl monobenzylidenesuccinate (0.05 mol) and the appropriate aromatic aldehyde (0.05 mol) in dry *t*-butanol (25 ml) was added to a stirred solution of potassium *t*-butoxide (from metallic potassium 0.05 mol in dry *t*-butanol, 45 ml) during 20 min. After heating under reflux for 1 hr the solvent was distilled off under reduced pressure. 4% aq KOH (150 ml) added and the mixture heated on a water-bath for 2 hr. The dark liquid was extracted with chloroform, the aqueous layer carefully acidified with conc HCl and the precipitated diacid collected, crystallised and characterised.

(*E*)-6-*Bromopiperonylidenesuccinic acid* obtained by Stobbe condensation of 6-bromopiperonal (11 g) on crystallisation from benzene came as colourless plates (13 g), m.p. 163° (lit.[9] 165-67°); diethyl ester by EtOH $-H_2SO_4$ method (8 hr refluxed); crystallised from hexane-benzene as yellow needles (7 g), m.p. 92°; UV($CHCl_3$): 245, 290; IR: 1740-1710 br (ester-C=O), 1650, 1510, 930; PMR(CCl_4): 1.22 (*t*, 3H, $CH_2COOCH_2CH_3$), 1.30 (*t*, 3H, $COOCH_2CH_3$), 3.22 (*s*, 2H, $CH_2COOCH_2CH_3$), 4.10 (*q*, 2H, $CH_2COOCH_2CH_3$), 4.20 (*q*, 2H, $COOCH_2CH_3$), 5.90 (*s*, 2H, $-OCH_2O-$), 6.79 (*s*, 1H, 6-ArH), 6.94 (*s*, 1H, 3-ArH), 7.58 (*s*, 1H, olefinic) (Found: C, 50.0; H, 4.4. $C_{16}H_{17}O_6Br$ requires C, 49.9; H, 4.5%).

(*E*)-6-*Bromoveratrylidenesuccinic acid* obtained by Stobbe condensation of 6-bromoveratraldehyde (12.25 g) on crystallisation from ethyl acetate came as colourless plates (13 g), m.p. 168° (lit.[8] 168-69°); diethyl ester (H_2SO_4-EtOH method, 8 hr refluxed) crystallised from hexane-benzene as light yellow needles (7.5 g), m.p. 74°; UV(EtOH): 240, 288; IR: 1720 (ester −C=O), 1630; PMR (CCl_4): 1.26 (*t*, 3H, $CH_2COOCH_2CH_3$), 1.34 (*t*, 3H, $COOCH_2CH_3$), 3.32 (*s*, 2H, $CH_2COOCH_2CH_3$), 3.74 (*s*, 3H, Ar−OMe), 3.84 (*s*, 3H, Ar−OMe), 4.14 (*q*, 2H, $CH_2COOCH_2CH_3$), 4.26 (*q*, 2H, $COOCH_2CH_3$), 6.99 (*s*, 2H, ArH), 7.74 (*s*, 1H, olefinic) (Found: C, 50.9; H, 5.3. $C_{17}H_{21}O_6Br$ requires C, 50.9; H, 5.3%).

(E)-6-Bromopiperonylidene-(E)-veratryl-idenesuccinic acid

It was obtained by the Stobbe condensation of diethyl (*E*)-6-bromopiperonylidene succinate (2 g, 0.005 mol) and veratraldehyde (0.85 g, 0.005 mol). It crystallised from ethyl acetate as colourless plates (2.5 g), m.p. 142°; UV(EtOH): 230, 280, 310; IR: 3600 (−COOH), 3000-2900 br, 1760-1660 br (acid −C=O), 1600, 930-910 br; PMR(CF_3COOH): 3.92 (*s*, 3H, 3'-OMe), 3.97 (*s*, 3H, 4'-OMe), 5.92 (*s*, 2H, $-OCH_2O-$), 6.82-7.22 (*m*, 5H, ArH), 8.08 (*s*, 1H, 7-H), 8.40 (*s*, 1H, 7'-H) (Found: C, 52.9; H, 3.6. $C_{21}H_{17}O_8Br$ requires C, 52.9; H, 3.6%).

(E)-6-Bromoveratrylidene-(E)-piperonyl-idenesuccinic acid

Stobbe condensation of diethyl (*E*)-6-bromoveratrylidene succinate (2 g, 0.005 mol) and piperonal (0.75 g, 0.005 mol) provided the title acid which crystallised from ethyl acetate as light yellow plates (2.4 g), m.p. 195°; UV(EtOH): 230, 285, 320; IR: 3000-2500 br (acid −OH), 1690-1650 br (acid −C

=O), 1590; PMR (CF_3COOH): 3.72 (*s*, 3H, 3′−OMe), 3.92 (*s*, 3H, 4′−OMe), 6.01 (*s*, 2H, $-OCH_2O-$), 6.82-7.30 (*m*, 5H, ArH), 8.02 (*s*, 1H, 7′−H), 8.39 (*s*, 1H, 7-H) (Found: C, 52.8; H, 3.6. $C_{21}H_{17}O_8Br$ requires C, 52.9; H, 3.6%).

(E)-6-Bromopiperonylidene-(E)-veratryl-idenesuccinic anhydride (Ib)

(*E*)-6-Bromopiperonylidene-(*E*)-veratrylidene-succinic acid (2 g) was refluxed with acetyl chloride (20 ml) for 1 hr, concentrated *in vacuo* and the residue crystallised from benzene as orange red needles (1.5 g), m.p. 238°; UV($CHCl_3$): 242, 310, 390, 480; IR: 1815, 1765 (anhydride −C=O), 1595, 1520, 927; PMR(CF_3COOH): 3.86 (*s*, 3H, Ar−OMe), 3.92 (*s*, 3H, Ar−OMe), 5.81 (*s*, 2H, $-OCH_2O-$), 5.75, 6.5, 6.7, 7.02 (4*s*, 5H, ArH), 8.06 (*s*, 1H, olefinic), 8.10 (*s*, 1H, olefinic) (Found: C, 54.9; H, 3.3. $C_{21}H_{15}O_7Br$ requires C, 54.9; H, 3.3%).

(E)-6-Bromoveratrylidene-(E)-piperonylidene-succinic anhydride (Ic)

Ic was prepared as above from (*E*)-6-bromoveratrylidene-(*E*)-piperonylidenesuccinic acid and crystallised from benzene as orange red needles (1.3 g), m.p. 240°; UV($CHCl_3$): 250, 320, 480; IR: 1810, 1760 (anhydride −C=O), 1585; PMR(CF_3COOH): 3.49 (*s*, 3H, Ar−OMe), 3.90 (*s*, 3H, Ar−OMe), 5.89 (*s*, 2H, $-OCH_2O-$), 6.02, 6.28, 6.48, 7.07 (4*s*, 5H, ArH), 7.90 (*s*, 1H, olefinic), 8.00 (*s*, 1H, olefinic) (Found: C, 55.0; H, 3.3. $C_{21}H_{15}O_7Br$ requires C, 54.9; H, 3.3%.

Thermal cyclisation of (E,E)-dibenzylidene-succinic anhydrides: General procedure

Anhydride (0.0025 mol) was dissolved in diphenyl ether (20 ml) and refluxed at 260° for 45 min. To this was added hexane (200 ml), the precipitated product filtered, repeatedly washed with hexane to remove the traces of diphenyl ether, dried *in vacuo* and subjected to appropriate method of separation and the individual components were characterised.

Photocyclisation of (E,E) dibenzylidene-succinic anhydrides: General procedure

The anhydride (0.0025 mol) in benzene (300 ml) containing a little iodine (200 mg) was irradiated in a pyrex tube with a medium pressure mercury lamp (100 W). The course of the reaction was followed by the disappearance of UV maxima at 320 and 480 nm. The reaction was complete in 10 hr.

Products obtained from thermal and photochemical cyclisation of Ia

Thermal cyclisation of Ia gave a mixture of products (950 mg), which were separated by column chromatography over silica gel. The fractions eluted with benzene-ethyl acetate (9:1) afforded 1-(3′,4′-dimethoxyphenyl)-6,7-methylenedioxynaphthalene-2,3-dicarboxy anhydride (IVa) as pale yellow needles (70 mg), m.p. 285° (lit.[1] 267-68°); UV(EtOH): 215, 258, 290; IR: 1830, 1770 (anhydride −C=O), 1460, 940. Ethyl acetate fractions yielded 1-(3′,4′-methylene-dioxyphenyl)-6,7-dimethoxynaphthalene-2,3-dicarboxy anhydride (IVb) as pale yellow needles (25 mg), m.p. 310-11° (lit.[1] 287-88°, which might probably be a mixture of IVa and IVb); UV(EtOH): 240, 290; IR: 1830, 1760 (anhydride −C=O); PMR(CF_3COOH): 3.96 (*s*, 3H, 6-OMe), 4.20 (*s*, 3H, 7-OMe), 6.12 (*s*, 2H, $-OCH_2O$), 6.92-7.18 (*m*, 3H, 2′,5′,6′-ArH), 7.46 (*s*, 1H, 8-ArH), 7.63 (*s*, 1H, 5-ArH), 8.55 (*s*, 1H, C_4-H) (Found: C, 66.6; H, 3.7. $C_{21}H_{14}O_7$ requires C, 66.7; H, 3.7%).

The other fractions yielded only a mixture of the anhydrides (IVa + IVb).

1-(3′,4′-Dimethoxyphenyl)-6,7-methylene-dioxynaphthalene-2,3-dicarboxylic acid (Va) and dimethyl ester (Ve)

The anhydride (IVa, 30 mg) was hydrolysed with 10% aq KOH, usual work-up provided Va which crystallised from ethyl acetate as colourless needles (25 mg), m.p. 286° (lit.[1] 155-60°, which might also be a mixture); UV(EtOH): 250; IR: 3400-2900 br, 1730-1670 br (acid −C=O), 1520, 940 (Found: C, 63.5; H, 4.0. $C_{21}H_{16}O_8$ requires C, 63.6, H, 4.1%); dimethyl ester (Ve) (diazomethane method), m.p. 248-50° (chloroform-hexane) (lit.[1] m.p. 139-40°); IR: 1735 (ester −C=O). Ester (Ve) was also obtained from the mixture of anhydrides (IVa + IVb, 850 mg) left over from the column. The mixture was hydrolysed with 10% aq KOH (100 ml) and the diacid mixture obtained esterified (diazomethane) and ester crystallised from benzene to pure Ve (300 mg), m.p. 248-50°, leaving a (1:1) mixture (450 mg) of the diesters (Ve and Vf).

1-(3′,4′-Methylenedioxyphenyl)-6,7-dimethoxy-naphthalene-2,3-dicarboxylic acid (Vb) and dimethyl ester (Vf)

The anhydride (IVb, 20 mg) was hydrolysed with 10% aq KOH (5 ml) and the diacid obtained was crystallised from ethyl acetate as colourless needles (18 mg), m.p. 305° (lit.[1] 165-70°); IR: 3400-2800 br, 1730-1670 br (acid −C=O) (Found: C, 63.5; H, 4.0. $C_{21}H_{16}O_8$ requires C, 63.6; H, 4.1%); dimethyl ester (Vf) (diazomethane method), semi-solid; UV($CHCl_3$): 250; IR($CHCl_3$): 1725 (ester −C=O), 1470, 1040; PMR(CCl_4): 3.56 (*s*, 3H, 2-COOMe), 3.67 (*s*, 3H, 6-OMe), 3.83 (*s*, 3H, 3-COOMe), 3.86 (*s*, 3H, 7-OMe), 5.97 (*s*, 2H, $-OCH_2O-$), 6.58-7.08 (*m*, 5H, ArH), 8.20 (*s*, 1H, C_4-H) (Found: C, 65.1; H, 4.7. $C_{23}H_{20}O_8$ requires C, 65.1; H, 4.8%).

2,3-Bis-(hydroxymethyl)-6,7-dimethoxy-1-(3',4'-methylenedioxyphenyl)naphthalene (Vk)

The above ester mixture (Ve + Vf, 250 mg) in anhydrous ether (150 ml) was reduced with $LiAlH_4$ (1.5 g) by stirring it at room temperature for 12 hr. After usual work-up the product obtained was separated by column chromatography into the isomeric diols Vj (80 mg) [colourless needles, m.p. 210-11 (lit.[16] 183)] and Vk (90 mg) [colourless needles, m.p. 187 (lit.[16] 191)]; UV($CHCl_3$): 245, 290; IR: 3300 br (−OH), 1500, 1430, 1035, 1005; PMR($CDCl_3$): 3.76 (*s*, 3H, 6-OMe), 4.01 (*s*, 3H, 7-OMe), 4.65 (*s*, 2H, 2-CH_2OH), 4.93 (*s*, 2H, 3-CH_2OH), 6.07 (*s*, 2H, $-OCH_2O-$), 6.77-7.36 (*m*, 5H, ArH), 7.72 (*s*, 1H, C_4-H) (Found: C, 68.5; H, 5.5. $C_{21}H_{20}O_6$ requires C, 68.5; H, 5.5%).

2,3-Bis-(methoxymethyl)-6,7-dimethoxy-1-(3],4'-methylenedioxyphenyl)naphthalene (Vl)

Compound (Vk, 50 mg) was dissolved in minimum amount of DMF and to it was added a fine powder of silver oxide (250 mg). Methyl iodide (2 ml) was added dropwise during 10 min and the flask kept in an ice-bath for 24 hr. The reaction product was filtered and the residue washed well with chloroform. The filtrate was poured into water (100 ml) and extracted with chloroform (3 × 20 ml). The chloroform layer was first washed repeatedly with aq KCN (0.1 *M*) and then with water. The chloroform layer was dried ($MgSO_4$) and evaporated to afford a mixture of methyl ethers (45 mg). This mixture was separated by preparative TLC into three pure components A, B and C (R_f: 0.65, 0.42 and 0.35 respectively). Component-A came as semi-solid (15 mg) and identified as Vl; UV($CHCl_3$): 250, 280, 330; IR($CHCl_3$): 1460, 1140, 1040, 930; PMR($CDCl_3$): 3.29 (*s*, 3H, 2-CH_2OMe), 3.49 (*s*, 3H, 3-CH_2OMe), 3.75 (*s*, 3H, 6-OMe), 4.00 (*s*, 3H, 7-OMe), 4.37 (*s*, 2H, 2-CH_2OMe), 4.77 (*s*, 2H, 3-CH_2OMe), 6.10 (*s*, 2H, $-OCH_2O-$), 6.62-7.30 (*m*, 5H, ArH), 7.82 (*s*, 1H, C_4-H) (Found: C, 69.6; H, 6.1. $C_{23}H_{24}O_6$ requires C, 69.7; H, 6.1%).

Component-B also came as a semi-solid (6 mg) and identified as 2-hydroxymethyl-3-methoxymethyl-6,7-dimethoxy-1-(3',4'-methylenedioxyphenyl-naphthalene (Vn); UV($CHCl_3$): 250, 285, 325; IR($CHCl_3$): 3500-3300 br, 2925, 1670, 1468, 1152, 1038, 930, 885; PMR($CDCl_3$): 3.48 (*s*, 3H, 3-CH_2OMe), 3.76 (*s*, 3H, 6-OMe), 4.02 (*s*, 3H, 7-OMe), 4.54 (*s*, 2H, 2-CH_2OH), 4.76 (*s*, 2H, 3-CH_2OMe), 6.06 (*d*, 2H, $-OCH_2O-$), 6.80-7.30 (*m*, 5H, ArH), 7.71 (*s*, 1H, C_4-H) (Found: C, 69.0; H, 5.8. $C_{22}H_{22}O_6$ requires C, 69.1; H, 5.8%).

Component-C also came as semi-solid (7 mg) and was identified as 2-methoxymethyl-3-hydroxymethyl-6,7-dimethoxy-1-(3',4'-methylenedioxyphenyl)naphthalene (Vm); UV($CHCl_3$): 250, 285, 325; IR($CHCl_3$): 3640 sh, 2940, 1670, 1467, 1330, 1152, 1010, 930, 890; PMR($CDCl_3$): 3.29 (*s*, 3H, 2-CH_2OMe), 3.74 (*s*, 3H, 6-OMe), 4.00 (*s*, 3H, 7-OMe), 4.33 (*s*, 2H, 2-CH_2OMe), 4.80 (*s*, 2H, 3-CH_2OH), 6.07 (*s*, 2H, $-OCH_2O-$), 6.75-7.35 (*m*, 5H, ArH), 7.75 (*s*, 1H, C_4-H) (Found: C, 69.1; H, 5.8. $C_{22}H_{22}O_6$ requires C, 69.1; H, 5.8%).

Ia (500 mg) on photochemical cyclisation gave a mixture of products, which were on fractional crystallisation from benzene gave pure IVb (70 mg). The remaining mixture of anhydrides (350 mg) was hydrolysed with 10% aq KOH to afford a mixture of diacid, which esterified (diazomethane). The ester mixture was reduced with $LiAlH_4$ and the diols obtained separated by column chromatography into Vj (110 mg) and Vk (95 mg) described above.

Products obtained from thermal and photochemical cyclisation of Ib

The anhydride Ib (1 g) on thermal cyclisation gave a mixture of products, which were crystallised from acetone to yield 1-(3',4'-dimethoxylphenyl)-6,7-methylenedioxynaphthalene-2,3-dicarboxy anhydride (IVa, 200 mg) as pale yellow needles, m.p. and m.m.p. 285°. The mother liquor on further concentration yielded yellow needles (355 mg) of 1-(2'-bromo-4',5'-methyelenedioxyphenyl)-6,7-dimethoxynaphthalene-2,3-dicarboxyanhydride (IVc), m.p. 252°; UV(EtOH): 230, 288; IR: 1830, 1760 (anhydride −C=O), 1600; PMR(CF_3COOH): 3.99 (*s*, 3H, 6-OMe), 4.20 (*s*, 3H, 7-OMe), 6.14 (*s*, 2H, $-OCH_2O-$), 6.90 (*s*, 1H, 6'-ArH), 7.23 (*s*, 1H, 3'-ArH), 7.33 (*s*, 1H, 8-ArH), 7.69 (*s*, 1H, 5-ArH), 8.60 (*s*, 1H, C_4-H) (Found: C, 55.1; H, 2.9; $C_{21}H_{13}O_7Br$ requires C, 55.2; H, 2.9%).

The mother liquor consisting of a mixture of IVa and IVc was hydrolysed with 10% aq KOH and the resulting diacid mixture esterified with diazomethane. The diester mixture thus obtained was separated by preparative TLC into two pure components Ve (30 mg), m.p. 248° and Vg (40 mg), m.p. 230°.

1-(2'-Bromo-4',5'-methylenedioxyphenyl)-6,7-dimethoxynaphthalene-2,3-dicarboxylic acid (IVc)

The anhydride (IVc, 300 mg) was hydrolysed with 10% aq KOH to give the diacid which crystallised from ethyl acetate as colourless plates (250 mg), m.p. 200°; UV(EtOH): 250, 370; IR: 3300, 1740, 1690 (acid −C=O) (Found: C, 53.0; H, 3.2. $C_{21}H_{15}O_8Br$ requires C, 53.1; H, 3.2%); dimethyl ester (Vg) of Vc obtained via diazomethane method crystallised from hexane-chloroform as colourless needles (180 mg), m.p. 230°; UV($CHCl_3$): 235, 258, 300; IR: 1720 (ester −C=O), 1620; PMR($CDCl_3$): 3.68 (*s*, 3H, 2-COOMe), 3.80 (*s*, 3H, 6-OMe), 3.93 (*s*, 3H, 3-COOMe), 4.02 (*s*, 3H, 7-OMe), 6.10 (*s*, 2H, $-OCH_2O-$), 6.67 (*s*, 1H, 6'-ArH), 6.82 (*s*, 1H, 3'-ArH), 7.19 (*s*, 1H, 8-ArH), 7.29 (*s*, 1H, 5

ArH), 8.50 (*s*, 1H, C_4-H) (Found: C, 54.8; H, 3.8. $C_{23}H_{19}O_8Br$ requires C, 54.9; H, 3.8%).

The product mixture obtained from Ib (100 mg) on photochemical cyclisation was as such hydrolysed with 10% aq KOH and the resulting diacid mixture (65 mg) esterified with diazomethane. The ester mixture was separated by preparative TLC into two pure components Ve (10 mg, m.p. and m.m.p. 248°) and Vg (15 mg, m.p. and m.m.p. 230°).

Products obtained from thermal and photochemical cyclisation of Ic

The product mixture obtained on thermal cyclisation of Ic (500 mg) was crystallised from acetone to yield the anhydride (IVb, 100 mg), m.p. 310°. The mother liquor on further concentration yielded the anhydride (IVd) as colourless needles (150 mg), m.p. 265°, identified as 1-(2′-bromo-4′,5′-dimethoxyphenyl)-6,7-methylenedioxynaphthalene-2,3-dicarboxy anhydride from the spectral data; UV($CHCl_3$): 235, 260, 285; IR: 1835, 1770, (anhydride $-C=O$); PMR(CF_3COOH): 3.88 (*s*, 3H, 5′-OMe), 4.02 (*s*, 3H, 4′-OMe), 6.20 (*s*, 2H, $-OCH_2O-$), 6.80 (*s*, 1H, 8-ArH), 6.96 (*s*, 1H, 5-ArH), 7.30 (*s*, 1H, 6′-ArH), 7.42 (*s*, 1H, 3′-ArH), 8.40 (*s*, 1H, C_4-H) (Found: C, 55.1; H, 2.8. $C_{21}H_{13}O_7Br$ requires C, 55.2; H, 2.9%).

1-(2′-Bromo-4′,5′-dimethoxyphenyl)-6,7-methylene-dioxynaphthalene 2,3-dicarboxylic acid (Vd)

The anhydride (IVd, 100 mg) was hydrolysed with 10% aq KOH (50 ml) and the diacid (80 mg) formed was crystallised from ethyl acetate as colourless plates m.p. 220°; UV(EtOH): 250, 290, 340; IR: 3400-3300 br, 1760, 1600 (acid $-C=O$) (Found: C, 53.1; H, 3.2. $C_{21}H_{15}O_8Br$ requires C, 53.1; H, 3.2%). Dimethyl ester (Vh) of Vd was prepared as usual (diazomethane method) and crystallised from hexane-chloroform as colourless plates (40 mg), m.p. 230°; UV($CHCl_3$): 255, 290; IR: 1730-1710 br (ester $-C=O$), 1600, 1500; PMR(CCl_4): 3.56 (*s*, 3H, 2-COOMe), 3.79 (*s*, 3H, 5′-OMe), 3.91 (*s*, 6H, 3-COOMe and 4′-OMe), 6.03 (*s*, 2H, $-OCH_2O-$), 6.61 (*s*, 1H, 8-ArH), 6.74 (*s*, 1H, 5-ArH), 7.06 (*s*, 1H, 6′-ArH), 7.13 (*s*, 1H, 3′-ArH), 8.30 (*s*, 1H, C_4-H) (Found: C, 54.9; H, 3.8. $C_{23}H_{19}O_8Br$ requires C, 54.9; H, 3.8%).

The anhydride Ic (350 mg) on photochemical cyclisation gave a mixture of products. It was resolved into 3 pure components; IVb (10 mg, m.p. and m.m.p. 310°), IVd (200 mg, m.p. and m.m.p. 265°) and a new derivative, which was identified as 1-(3′,4′-methylene-dioxyphenyl)-5-bromo-7,8-dimethoxynaphthalene-2,3-dicarboxyanhydride (IVe, 20 mg), m.p. 260°; UV($CHCl_3$): 235, 260, 290; IR: 1830, 1770 (anhydride $-C=O$), 1580; PMR(CF_3COOH): 3.45 (*s*, 3H, 8-OMe), 4.11 (*s*, 3H, 7-OMe), 6.04 (*s*, 2H, $-OCH_2O-$), 6.61-6.90 (*m*, 3H, ArH), 7.99 (*s*, 1H, 6-ArH), 8.98 (*s*, 1H, C_4-H) (Found: C, 55.2; H, 2.9. $C_{21}H_{13}O_7Br$ requires C, 55.2; H, 2.9%). Dimethyl ester (Vi) of IVe was prepared as usual (diazomethane method) and crystallised from hexane-chloroform as colourless needles (11 mg), m.p. 160°; UV($CHCl_3$): 235, 260, 290; IR: 1720, (ester $-C=O$), 1580; PMR(CCl_4): 3.21 (*s*, 3H, 8-OMe), 3.51 (*s*, 3H, 2-COOMe), 3.92 (*s*, 6H, 3-COOMe and 7-OMe), 5.97 (*s*, 2H, $-OCH_2O-$), 6.55-6.75 (*m*, 3H, ArH), 7.61 (*s*, 1H, 6-ArH), 8.82 (*s*, 1H, C_4-H) (Found: C, 54.8; H, 3.8. $C_{23}H_{19}O_8Br$ requires C, 54.9; H, 3.8%).

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Synthesis of (*S*)-Hydroxyethyl-γ-butyrolactone & Its Application to the Synthesis of *R*(+)-γ-Caprolactone†

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Synthesis of *S*-hydroxyethyl-γ-butyrolactone, as a chiral building block for natural product synthesis, is described. Its utility in the synthesis of naturally occurring *R*(+)-caprolactone, a pheromone of *Trogoderma* species of dermestid bettles, is reported.

In pursuit of our efforts[1] to synthesise chiral building blocks from carbohydrates, we realised that optically active hydroxyethyl-γ-butyrolactone would serve as an important chiral synthon for the synthesis of a number of natural products. Although *R*- and *S*- hydroxymethyl-γ-butyrolactones have been frequently utilised[2] in natural product chemistry, to the best of our knowledge, no report for chiral *S*-hydroxyethyl-γ-butyrolactone (**1**) has appeared so far. However, racemic **1** had been prepared earlier[3]. We now describe an enantiospecific synthesis of *S*-**1** starting from D-glucose, and report its utility in the synthesis of *R*(+)-γ-caprolactone[4], a pheromone[5] of several *Trogoderma* species of dermestid beetles.

3-Iodo-3-deoxy-1,2,5,6-di-O-isopropylidene-α-D-allo-furanose (**3**) was prepared from diacetone-glucose (**2**) by Garreggs' procedure[6]. We have observed that for large scale preparation of **3** vigorous stirring was most essential in order to get consistent yield > 65%. Reductive de-iodination[7] of **3** to the deoxy compound[8] (**4**) in 95% yield was achieved using 1 molar % of tri-*n*-butyltin chloride and excess of sodium borohydride with irradiation from a 100 watt tungsten lamp. The characteristic signals for H-3,3′ protons were observed at δ 2.0 in the PMR spectrum of **4**.

Selective hydrolysis of the 5,6-isopropylidene functionality in **4** was effected with 0.8% aq sulfuric acid in methanol to give the diol[8] (**5**) which was mesylated to **6** and then treated with sodium iodide in refluxing ethyl methyl ketone to furnish the 5,6-ene (**7**) in an overall 44% yield. Hydroboration of **7** with diborane in tetrahydrofuran at 0° followed by oxidation with hydrogen peroxide gave the alcohol[9] (**8**) in 76% yield. The PMR spectrum of **8** revealed a triplet for H-6,6 protons at δ 3.80. The hydroxyl group in **8** was protected as its benzyl ether (**9**).

Treatment of **8** with methanolic hydrogen chloride under reflux furnished the methyl glycoside (**10**) in 92% yield. PMR spectrum of **10** was compatible with the assigned structure and also suggested that **10** was a mixture of α- and β-glycosides in which β-isomer was a major isomer. Deoxygenation of the 2-hydroxy group in **10** was conveniently effected using Barton's procedure[10]. For example, **10** was converted into its xanthate derivative (**11**) by conventional procedure. The downfield shift of H-2 proton in the PMR spectrum of **11** clearly proved that xanthate function was present at this carbon. Treatment of **11** with freshly prepared tri-*n*-butyltin hydride in refluxing toluene gave the deoxy product (**12**) in 76% yield.

Compound **12** was converted into the lactone (**13**) by two procedures. In a direct approach[11], the methyl glycoside (**12**) was treated with *m*-perchlorobenzoic acid in the presence of borontrifluoride etherate in methylene chloride at room temperature when **13** was obtained in 74% yield whose structure was unequivocally proved by IR and PMR spectra. In the second approach, the **12** was first hydrolysed with aq acetic acid to the hemiacetal (**14**) which was subsequently oxidised with pyridium chlorochromate to **13** in 70% yield.

Hydrogenolysis of **13** with 10% Pd/C yielded the desired *S*-hydroxyethyl-γ-butyrolactone (**1**) in 78% yield. Having obtained the target **1** in an optically active form, we ventured on its application for the synthesis of naturally occurring sex attractant pheromone[5], *R*(+)-γ-caprolactone (**17**).

Compound **1** was treated with methanesulfonyl chloride-pyridine mixture to afford the mesylate (**15**) in 74% yield. In the PMR spectrum of **15** the downfield shift of 0.56 ppm for a triplet due to H-6,6 protons as compared to that in **14** clearly indicated that mesyloxy function was present at this carbon. Nucleophilic displacement reaction of **15** with sodium iodide in refluxing acetone afforded the 6-iodide (**16**) whose

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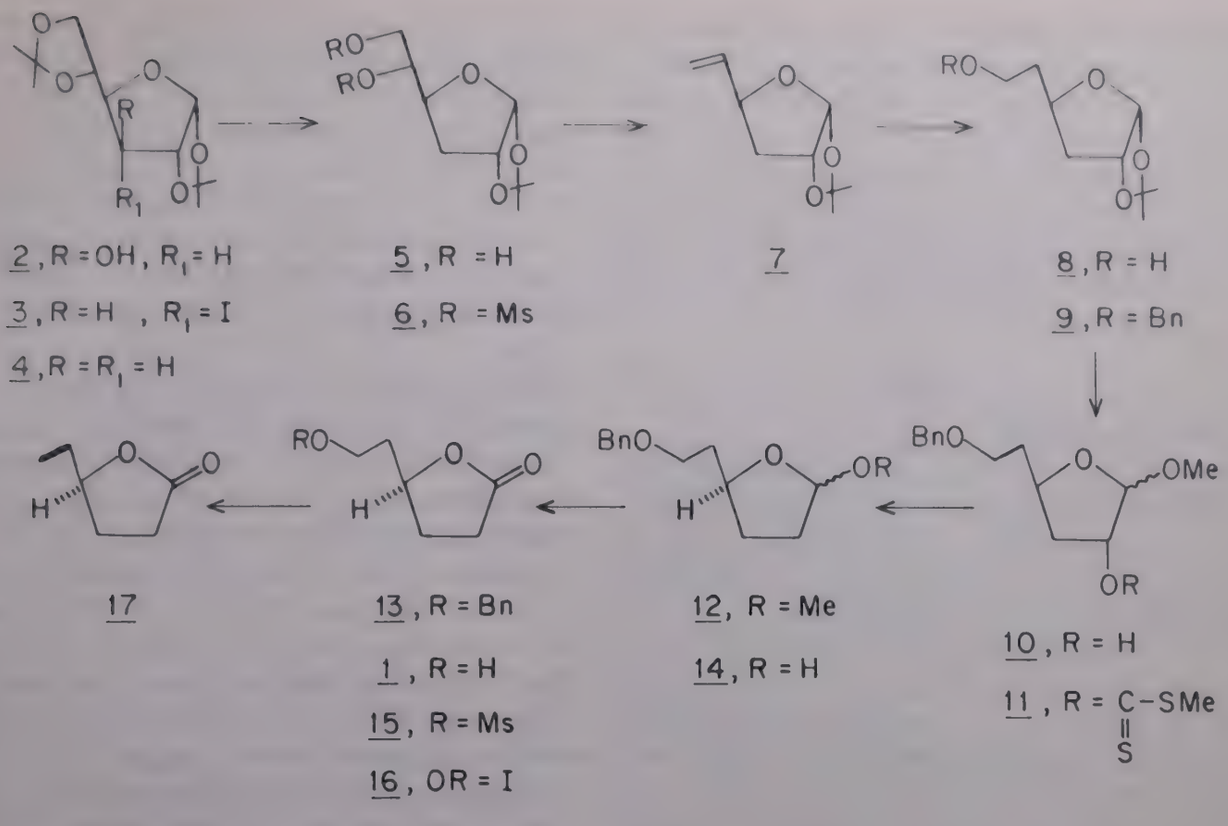

structure was proved by PMR spectrum. For instance, the loss of mesyl singlet was clearly visible. In addition, the triplet due to H-6,6′ showed an upfield shift of 1.11 ppm as compared to that of **15**. This was expected because of shielding effect of the iodide group. Reduction of **15** with tri-*n*-butyltin hydride was facile giving *R*(+)-γ-caprolactone (**17**) whose ^{1}H-nmr and other physical data[4] coincided well with those of the natural sample.

Applications of **S-1** for the synthesis of other natural products are in progress and will be reported elsewhere.

Experimental Procedure

3-Deoxy-(1,2:5,6)-di-O-isopropylidene-α-D-ribohexofuranose (**4**)

To a stirred solution of **3** (7.4 g, 20 mmol) in dry methanol (100 ml) was added tri-*n*-butyltin chloride (65 mg) and the solution irradiated with 100 watt tungsten lamp. Solid sodium borohydride (1.14 g, 30 mmol) was added gradually during 1 hr with TLC monitoring. Solvent was removed under reduced pressure and the residue partitioned between ethyl acetate and water. The ethyl acetate layer was dried, concentrated and the product chromatographed over silica gel column. Elution with ethyl acetate-light petroleum (gradient: 1:10; 1:2) gave **4** (4.6 g, 96%); $[\alpha]_D -5.6°$ (*c*, 4.1, ethanol) (lit.[8] $[\alpha]_D -5.78$ (ethanol); PMR (CCl_4): δ 1.23, 1.33, 1.43 (3*s*, 12H, 2 × CMe_2), 1.5-2.4 (*m*, 2H, H-3,3′), 3.5-4.1 (*m*, 4H, H-4,5,6,6′), 4.53 (*t*, 1H, H-2, J = 4 Hz), 5.53 (*d*, 1H, H-1, J = 4 Hz).

3-Deoxy-1,2-O-isopropylidene-α-D-ribohexofuranose (**5**)

Compound (**4**, 3 g, 12.28 mmol) in methanol (35 ml) and 0.8% aq sulfuric acid (12 ml) was stirred at room temperature for 24 hr. The reaction was neutralised with solid barium carbonate, filtered and the filtrate concentrated to afford **5** (2 g, 80%), which crystallised from chloroform-light petroleum, m.p. 80° (lit. m.p. 84°); $[\alpha]_D -13.3°$ (*c*, 0.8, chloroform).

3-Deoxy-1,2-O-isopropylidene-5,6-di-O-mesyl-α-D-ribohexofuranose (**6**)

To a stirred solution of **5** (2.0 g, 9.8 mmol) in dry pyridine (20 ml) at 0° was added methanesulfonyl chloride (8.4 g, 73.2 mmol). The reaction was allowed to attain room temperature. After 1.5 hr, the reaction was worked-up in conventional fashion and **6** (3 g, 85%) isolated, m.p. 87°; $[\alpha]_D +0.66°$ (*c*, 2.0, chloroform); PMR ($CDCl_3$): δ 1.30, 1.46 (2*s*, 6H, CMe_2), 2.0 (*m*, 2H, H-3,3′), 3.8-5.0 (*m*, 5H, H-2, 4,5,6,6′), 5.63 (*d*, 1H, H-1, J = 3 Hz) (Found: C, 36.9; H, 5.5. $C_{11}H_{20}O_9S_2$ requires C, 36.7; H, 5.6%).

3,5,6-Trideoxy-1,2-O-isopropylidene-α-D-erythro-hex-5-enofuranose (**7**)

A mixture of **6** (3.0 g, 8.32 mmol), sodium iodide (5.0 g, 33.2 mmol) and ethyl methyl ketone (50 ml) was heated under reflux for 8 hr. The reaction was concentrated and the residue partitioned between water and chloroform and the chloroform layer successively washed with sodium thiosulfate, sodium carbonate, water, dried and concentrated to afford a

product which was purified through a short column of silica gel using ethyl acetate-light petroleum (1:10) to give syrupy **7** (1.1 g, 78%); $[\alpha]_D$ −34.4° (*c*, 0.6, chloroform); PMR ($CDCl_3$):δ 1.33, 1.53 (2*s*, 6H, CMe_2), 1.4-2.3 (*m*, 2H, H-3,3'), 4.6 (*m*, 1H, H-4), 4.75 (*t*, 1H, H-2, J = 4 Hz), 5.17 (*dq*, 1H, H-6, J_{cis} = 10 Hz), 5.33 (*dq*, 1H, H-6', J_{trans} = 16 Hz), 5.6-6.1 (*o*, 1H, H-5), 5.86 (*d*, 1H, H-1, J = 3 Hz) (Found: C, 63.3; H, 8.1. $C_9H_{14}O_3$ requires C, 63.5; H, 8.2%).

3,5-Dideoxy-1,2-O-isopropylidene-α-D-erythrohexofuranose (**8**)

A solution of **7** (1.1 g, 6.46 mmol) in dry tetrahydrofuran (8 ml) was cooled to 0° under nitrogen and then to this was added 1 *M* solution of diborane in tetrahydrofuran (3 ml, 3 mmol). After 1.5 hr, methanol was carefully introduced to decompose excess of borane, followed by addition of 1 *M* aq sodium acetate (3 ml) and 30% hydrogen peroxide (1.8 ml). The reaction was stirred for 1 hr, solvent removed under reduced pressure and the residue partitioned between chloroform and water. The chloroform layer was concentrated and the residue purified by column chromatography on silica gel using ethyl acetate-light petroleum (1:1) to afford **8** (0.86 g, 76%); $[\alpha]_D$-7.1° (*c*, 0.7, chloroform) lit.[9] $[\alpha]_D$ −7.1° (chloroform); PMR ($CDCl_3$): δ 0.8-2.3 (*m*, 4H, H-3,3',5,5'), 1.31, 1.51 (2*s*, 6H, CMe_2), 3.80 (*t*, 2H, H-6,6', J = 6 Hz), 4.3 (*m*, 1H, H-4), 4.71 (*t*, 1H, H-2, J = 4 Hz), 5.80 (*d*, 1H, H-1, J = 4 Hz); MS *m/z* 188 (M^+), 173 ($M^+ - 15$) (Found: C, 57.1; H, 8.3. $C_9H_{16}O_4$ requires C, 57.4; H, 8.5%).

6-O-Benzyl-3,5-dideoxy-1,2-O-isopropylidene-α-D-erythro-hexofuranose (**9**)

The compound (**8**, 0.70 g, 3.7 mmol) was dissolved in dry tetrahydrofuran (10 ml) under nitrogen and to this was added in portions with stirring sodium hydride (50% oil dispersion, 0.36 g, 5.0 mmol). After 1.5 hr, benzyl bromide (0.88 g, 5.5 mmol) was introduced and stirred overnight. Methanol (2 ml) was carefully added and the mixture concentrated to dryness. The residue was chromatographed on a column of silica gel using ethyl acetate-light petroleum (gradient, 1:10; 1:4) to afford **9** (1.0 g, 97%); $[\alpha]_D$ + 1.7° (*c* 1, chloroform); PMR (CCl_4):δ 1.0-2.4 (*m*, 4H, H-3,3',5,5'), 1.31, 1.50 (2*s*, 6H, CMe_2), 3.50 (*t*, 2H, H-6,6', J = 6 Hz), 4.1 (*m*, 1H, H-4), 4.43 (*s*, 2H, $PhCH_2$), 4.56 (*t*, 1H, H-2, J = 4 Hz), 5.60 (*d*, 1H, H-1, J = 4 Hz), 7.16 (*s*, 5H, Ph) (Found: C, 68.7; H, 8.0. $C_{16}H_{22}O_4$ requires C, 69.0; H, 7.9%).

Methyl 6-O-benzyl-3,5-dideoxy-(α- and β-)-D-erythrohexofuranoside (**10**)

A solution of **9** (1.0 g, 3.6 mmol) in 1% methanolic hydrogen chloride (20 ml) was heated under reflux for 4 hr. Solid lead carbonate was added to neutralise the solution which was then filtered and concentrated. The residue was purified on a short column of silica gel using ethyl acetate-light petroleum (1:1) to afford **10** (0.84 g, 92%); PMR ($CDCl_3$) (β-isomer): δ1.7-2.1 (*m*, 4H, H-3,3',5,5'), 3.25 (*s*, 3H, OMe) 3.56 (*t*, 2H, H-6,6', J = 6 Hz), 4.0-4.8 (*m*, 2H, H-2,4), 4.43 (*s*, 2H, $PhCH_2$), 4.68 (*s*, 1H, H-1), 7.28 (*s*, 5H, Ph) (Found: C, 66.2; H, 8.1. $C_{14}H_{20}O_4$ requires C, 66.6; H, 7.9%).

Methyl 6-O-benzyl-3,5-dideoxy-2-methylthiocarbonyl (α- and β-)-D-erythrohexofuranoside (**11**)

To a stirred solution of **10** (0.84 g, 3.34 mmol) in dry tetrahydrofuran (5 ml) under nitrogen was added sodium hydride (50% oil dispersion, 0.66 g, 27.5 mmol) in small portions. The mixture was stirred for 1.5 hr, dry carbon disulphide (0.7 g, 9.2 mmol) was introduced and to this was added methyl iodide (1.5 g, 9.8 mmol) after 20 min. After 24 hr, methanol (2 ml) was carefully added, and the solution concentrated to afford a residue which was chromatographed on a column of silica gel using ethyl acetate-light petroleum (gradient, 1:10; 1:4) to give **11** (1.1 g, 94%); PMR ($CDCl_3$)(β-isomer): δ 1.4-2.4 (*m*, 4H, H-3,3',5,5'), 2.55 (*s*, 3H, SMe), 3.37 (*s*, 3H, OCH_3), 3.66 (*t*, 2H, H-6,6', J = 6 Hz), 4.4 (*m*, 1H, H-4), 4.46 (*s*, 2H, $PhCH_2$), 5.02 (*s*, 1H, H-1), 5.82 (*d*, 1H, H-2, J = 4 Hz), 7.37 (*s*, 5H, Ph); MS: *m/z* 342 (M^+), 310 ($M^+ - 32$) (Found: C, 56.1; H, 6.5. $C_{16}H_{22}O_4S_2$ requires C, 56.1; H, 6.5%).

Methyl 6-O-benzyl-2,3,5-trideoxy-(α,β)-D-glycerohexofuranoside (**12**)

To a solution of **11** (1.1 g, 3.15 mmol) in dry toluene (15 ml) containing α,α'-azobisisobutyronitrile (5 mg) was added freshly prepared tri-*n*-butyltin hydride (3 g, 10.3 mmol). After 6 hr, the reaction mixture was concentrated and the resulting residue chromatographed on a column of silica gel using ethyl acetate-light petroleum (gradient, 1:20; 1:9) to afford **12** (0.55 g, 73%); PMR ($CDCl_3$) (β-isomer): δ 0.7-2.2 (*m*, 6H, H-2,2', 3,3',5,5'), 3.31 (*s*, 3H, OCH_3), 3.62 (*t*, 2H, H-6,6', J = 6 Hz), 4.2 (*m*, 1H, H-4), 4.53 (*s*, 2H, $PhCH_2$), 4.95 (*m*, 1H, H-1), 7.37 (*s*, 5H, Ph); MS: *m/z* 236 (M^+), 205 ($M^+ - 31$) (Found: C, 71.0; H, 8.8. $C_{14}H_{20}O_3$ requires C, 71.2; H, 8.5%).

S-6-Benzyloxyethyl-γ-butyrolactone (**13**)

Procedure (a)—To the solution of **12** (0.26 g, 1.1 mmol) in dry methylene chloride (10 ml) under nitrogen was added borontrifluoride etherate (0.01 ml) and *m*-chloroperbenzoic acid (0.24 g, 1.38 mmol) at room temperature. After 2 hr of stirring, ether was added and the mixture washed with aq sodium thiosulfate, aq sodium carbonate, water, dried and concentrated. The residue was purified by passing

through a short column of silica gel with ethyl acetate-light petroleum (1:1) to afford **13** (0.18 g, 74%); $[\alpha]_D$ +41.5° (*c*, 0.6, chloroform); PMR ($CDCl_3$): δ 1.5-2.7 (*m*, 6H, H-2, 2',3,3',5,5'), 3.62 (*t*, 2H, H-6,6', *J*=6 Hz), 4.51 (*s*, 2H, $PhCH_2$), 4.7 (*m*, 1H, H-4), 7.35 (*s*, 5H, Ph); MS: *m/z* 220 (M^+); IR: 1775 cm^{-1} (lactone) (Found: C, 70.6; H, 7.0. $C_{13}H_{16}O_3$ requires C, 70.9, H, 7.2%).

Procedure (b)—**12** (0.21 g, 0.89 mmol) in 50% aq acetic acid (2 ml) was heated on a water-bath for 8 hr. The mixture was concentrated and then co-distilled several times with toluene to afford **14**, which was dissolved in methylene chloride and pyridium chlorochromate (0.3 g) added to it. After 24 hr, ether was added and the solution passed through a silica gel column. Elution with ethyl acetate-light petroleum (1:2) afforded **13** (0.135 g, 70%).

S-Hydroxyethyl-γ-butyrolactone (**1**)

Compound (**13**, 0.26 g, 1.18 mmol) in ethanol (10 ml) was hydrogenolysed in the presence of 10% Pd/C (70 mg) for 10 hr at normal pressure and temperature. The catalyst was filtered through a bed of celite, the filtrate concentrated and the residue purified on a short column of silica gel using ethyl acetate-light petroleum (1:1) to give **1** (0.12 g, 78%); $[\alpha]_D$ + 61.3° (*c*, 0.62, chloroform); PMR ($CDCl_3$): δ 1.0-2.8 (*m*, 6H, H-2,2',3,3',5,5'), 3.81 (*t*, 2H, H-6,6', *J* = 6 Hz), 4.6 (*m*, 1H, H-4); IR: 1760 (lactone), 3450(OH) cm^{-1} (Found: C, 55.1; H, 7.5. $C_6H_{10}O_3$ requires C, 55.4; H, 7.7%).

S-Mesyloxyethyl-γ-butyrolactone (**15**)

To a cooled solution (0°C) of **1** (0.11 g, 0.85 mmol) in pyridine (2 ml) was added methanesulfonyl chloride (1 ml). After 2.5 hr at room temperature the reaction was worked-up as usual and the crude product purified by column chromatography on silica gel using ethyl acetate-light petroleum (1:1) to give **15** (0.11 g, 74%); $[\alpha]_D$ + 75° (*c*, 0.7, chloroform); PMR ($CDCl_3$): δ 1.6-2.8 (*m*, 6H, H-2,2',3,3',5,5'), 3.00 (*s*, 3H, OMs), 4.37 (*t*, 2H, H-6,6' *J* = 6 Hz), 4.6 (*m*, 1H, H-4); IR: 1760 (lactone) cm^{-1}; MS: *m/z* 208.

S-Iodoethyl-γ-butyrolactone (**16**)

Compound (**15**, 0.1 g, 0.57 mmol) in dry acetone (5 ml) containing sodium iodide (0.2 g, 1.34 mmol) was heated under reflux for 8 hr. Solvent was removed under reduced pressure, the residue dissolved in chloroform and successively washed with aq sodium thiosulfate, aq sodium carbonate, water, dried and concentrated. The crude product was purified by column chromatography on silica gel using ethyl acetate-light petroleum (1:1) to yield **16** (0.12 g, 80%); $[\alpha]_D$ + 69.5° (c, 0.9, chloroform); PMR ($CDCl_3$): δ 1.3-2.8 (*m*, 6H, H-2,2',3,3',5,5'), 3.26 (*t*, 2H, H-6,6', *J* = 6 Hz), 4.6 (*m*, 1H, H-4); *m/z* 240 (M^+).

R(+)-γ-Caprolactone (**17**)

Compound (**16**, 0.12 g, 50 mmol) in dry benzene containing α,α'-azobisisobutyronitrile (2 mg) under nitrogen was heated under reflux. Freshly prepared tri-*n*-butyltin hydride (0.2 g) was introduced and after 8 hr, the reaction mixture was concentrated to dryness and the residue chromatographed on a short column of silica gel using ethyl acetate-light petroleum (gradient: 0:1, 1:1) to afford **17** (0.046 g, 80%); $[\alpha]_D$ + 50° (*c*, 1, methanol) lit.[4] $[\alpha]_D$ + 53° (methanol); PMR ($CDCl_3$): δ 1.00 (*t*, 3H, H-6,6',6'), 1.1-2.8 (*m*, 6H, H-2,2',3,3',5,5'), 4.37 (*m*, 1H, H-4); IR: 1770 (lactone) cm^{-1}; MS: *m/z* 114 (M^+) (Found: C, 62.9; H, 8.7. $C_6H_{10}O_2$ requires C, 63.1; H, 8.7%).

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Chemical Constituents of *Phyllanthus niruri* Linn.

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In addition to the known lignans, nirtetralin, niranthin, hypophyllanthin, phylltetralin, phyllanthin, lintetralin, a new phthalic acid bis-ester, designated as phyllester together with β-sitosterol, dotriacontanoic acid and a rare sterol, 24-isopropylcholesterol have been isolated from the hexane extract of the aerial parts of *Phyllanthus niruri* Linn. The structure of the phyllester has been elucidated as phthalic acid bis-2,5-dimethylhexyl) ester on the basis of spectral and chemical evidences.

A wide range of medicinal uses including treatment of jaundice, asthama and bronchial infections have been attributed to the extractives of *Phyllanthus niruri* Linn[1]. Extensive chemical studies on this plant has so far resulted in the isolation of lignans[2], flavonoids[3], triterpenoids[4,5] and alkaloids[5,6]. We have recently characterized various antihepatotoxic constituents[7] from the hexane extract, which on further chromatographic purification led to the isolation of known lignans namely, nirtetralin, niranthin, hypophyllanthin, phylltetralin, phyllanthin and lintetralin in addition to four more compounds designated as compounds A, B, C and D.

Compound-A obtained as a light yellow viscous mass, analysed for $C_{24}H_{38}O_4$. Its IR spectrum was indicative of the absence of an OH function, and the presence of an ester function and aromatic nucleus having a long chain aliphatic moiety possessing an isopropyl grouping respectively. In its PMR spectrum four aromatic protons appeared at δ 7.53 while two *gem*-dimethyl groups appeared as a 12-proton doublet at 0.9 (J = 6.5 Hz). The existence of an aliphatic side chain was discernible in the signals in the region 0.6 to 2.33. The ester methylene group appeared at 4.12 (*d*, J = 6 Hz).

Compound-A on alkaline hydrolysis yielded phthalic acid (co-TLC) and an alcohol (TLC) which could not be isolated due to the paucity of the material. Its complete structure was, however, elucidated on the basis of critical mass spectral analysis. Its mass spectrum exhibited molecular ion peak at m/z 390 followed by two prominent peaks at m/z 278 and 166 arising by the sequential loss of alcohol residue. This was confirmed by the presence of counter fragments at m/z 112 and 113 corresponding to C_8H_{16} and C_8H_{17} respectively. The structure of side chain could readily be deduced as 2,5-dimethyl-*n*-hexyl on the basis of the peaks at m/z 113, 99, 71, 57, 43 as shown in Fig. 1. Hence, on the basis of foregoing evidences structure of compound-A has been elucidated as phthalic acid, bis-(2,5-dimethylhexyl) ester

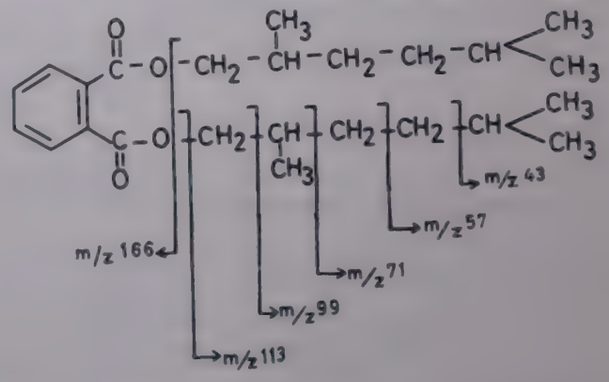

Fig. 1—Mass spectral fragmentation pattern of phyllester

Compound-B, m.p. 94° showed carboxylic group absorption at 1700 cm^{-1} in its IR spectrum and two triplets at δ 0.89 and 2.34 (J = 6 Hz) for CH_2-CH_3 and CH_2CH_2COOH groupings alongwith a broad singlet at δ 1.25 integrating for 6 OH in its PMR spectrum. This indicated that compound-B was a straight chain aliphatic acid. This was in full agreement with its mass spectrum which exhibited molecular ion peak at m/z 480 and a fragment at 435 corresponding to the loss of carboxylic group and other fragments due to sequential loss of fourteen mass units. Thus, it was identified as dotriacontanoic acid.

Compound-C, $C_{30}H_{52}O$ (M^+ 428) contained OH and *gem*-dimethyl functions as revealed by IR peaks at 3400 and 1372, 1365 cm^{-1} respectively. Its IR spectrum was flat in the carbonyl region. Its PMR spectrum indicated the presence of a trisubstituted olefinic unsaturation at δ 5.24 and an hydroxymethine as a broad singlet at 3.40 and an equatorially oriented hydroxyl. The presence of two tertiary methyls and five secondary methyls was revealed by the signals at δ 0.80 and 0.92 and doublets (J = 7 Hz) at 0.80 and 0.98. Its mass spectrum displayed strong molecular ion peak at m/z 428, in addition to fragments at m/z 413 $[M-Me]^+$ and m/z 395 $[M-Me-H_2O]^+$. The characteristic peak at m/z 274 for steroidal fragment ion[9] was generated by the loss of side chain. The peak at m/z 343 was strongly suggestive of the presence of a

isopropyl group which was confirmed by the appearance of an intense peak at m/z 42 corresponding to the isopropyl fragment ion. Thus, compound-D was identified as 24-isopropylcholesterol (**2**). It is worth mentioning here that this is the first report for its occurrence in higher plants as it has been earlier reported from sponges[10] and orchids[11].

Compound-D, was identified as β-sitosterol (m.m.p., co-TLC, IR).

Experimental Procedure

All melting points are uncorrected. IR spectra of compounds-A and C were recorded neat while those of B and D in KBr on a Perkin-Elmer 399B spectrophotometer. PMR spectra were recorded in $CDCl_3$ in a Varian FT-80A instrument using TMS as an internal standard; chemical shifts are in δ-scale. Both preparative and analytical TLC were carried out on silica gel G chromatoplate and iodine chamber was used to detect the spots.

The plant material was collected from the Institute farm during August 1983 and identified by the Botany Department of our Institute. A specimen No. 439 is also preserved in the herbarium.

Isolation

Dried powdered *P. niruri* (1 kg, aerial parts) was mixed with $Ca(OH)_2$ in 10:3 ratio extracted exhaustively with hexane and the hexane extract concentrated. The concentrate (30 g) was dissolved in hot hexane (1 litre) and MeOH (3 × 200 ml) added to obtain a precipitate (5 g). The filtrate was concentrated to yield a residue (25 g). The precipitate was chromatographed over silica gel (250 g) and eluted with hexane and with hexane containing increasing amounts of ethyl acetate. In all 200 fractions (250 ml each) were collected and mixed according to their TLC behaviour.

Compound-A

The combined fractions (8-15) on PLC (pet. ether-ethyl acetate, 96:4) yielded compound-A (12 mg) as a yellow viscous mass. R_f 0.63 (pet. ether-ethyl acetate, 94:6); IR: 2980, 2960, 2860, 1725, 1600, 1580, 1460, 1375, 1275, 1125, 1070, 1040, 960, 800, 745, 705, 650 and 610; PMR; 0.90 (*d*, 12H, $4 \times CH_3$, J=6.5 Hz), 0.60-2.33 (*m*, 18H), 4.12 (*d*, 4H, $2 \times CO-CH_2-CH$, J = 6 Hz), 7.53 (*m*, 4H, aromatic H); MS: m/z (M^+ 390), 278, 167, 149, 113, 112, 104, 99, 83, 71, 57, 43.

Alkaline hydrolysis of compound-A

Compound-A (5 mg) was refluxed with aq. KOH (2%) for 2 hr. Usual work-up afforded phthalic acid and an alcohol which showed a single spot on TLC.

Compound-B

The fraction (39-45) were kept in hexane which led to the isolation of compound-B as a crystalline solid (65 mg), m.p. 94°; R_f 0.14 (pet. ether-ethyl acetate, 85:15); IR: 2920, 2850, 1700, 1470, 1460, 1405, 1290, 729, 718; PMR: 0.89 (3H, *bt*, CH_2CH_3, J=6 Hz), 1.25 (60H, *s*), 2.34 (2H, *t*, CH_2-CH_2-COOH, J=6 Hz); MS: m/z 480 (M^+).

Isolation of compounds C and D

The part B (10 g) was fractionated over silica gel (300 g). The residue (25 mg) from the filtrate was fractionated over silica gel (300 g), eluting with hexane and hexane containing increasing amount of ethyl acetate. The total of 175 fractions (100 ml) were collected and mixed according to their TLC behaviour.

Compound-C

The combined fractions (16-27) (500 mg) were rechromatographed over silica gel. Elution with pet. ether-ethyl acetate (9:1) yielded compound-C as a colourless viscous mass (18 mg); R_f 0.55 (pet. ether-ethyl acetate, 9:1); IR: 3400, 2930, 2880, 1460, 1372, 1365, 1060, 1050; PMR: 0.80 (9H, *d*, $3 \times CH_3$, J=7Hz), 0.80 (3H, *s*, CH_3), 0.92 (3H, *s*, CH_3), 0.98 (6H, *d*, $2 \times CH_3$, J=7 Hz), 1.25-2.40 (*m*, 29H), 3.40 (1H, *bs*, H-3), 5.24 (1H, *d*, H-6, J=5 Hz); MS: m/z (M^+ 428), 413 (M − Me), 395 (M − Me − H_2O), 343 (M − 2 × Me_2CH), 325, 274, 271, 260, 256, 242, 230, 176, 164, 95, 81, 69, 55, 42.

Compound-D

The combined fraction (40-59) on crystallisation from methanol yielded compound-D (85 mg), m.p. 134°, which was identified as β-sitosterol by comparison with an authentic sample.

Other fractions yielded nirtetralin (87-100) niranthin (101-111), hypophyllanthin (112-117), phylltetralin (118-124), phyllanthin (125-136) and lintetralin (137-140) identified by their R_f values in specific solvents and characteristic colour with various spraying reagents[2].

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Optical Induction: Part VII†—Reaction between Phenyloxirane & Benzylamine

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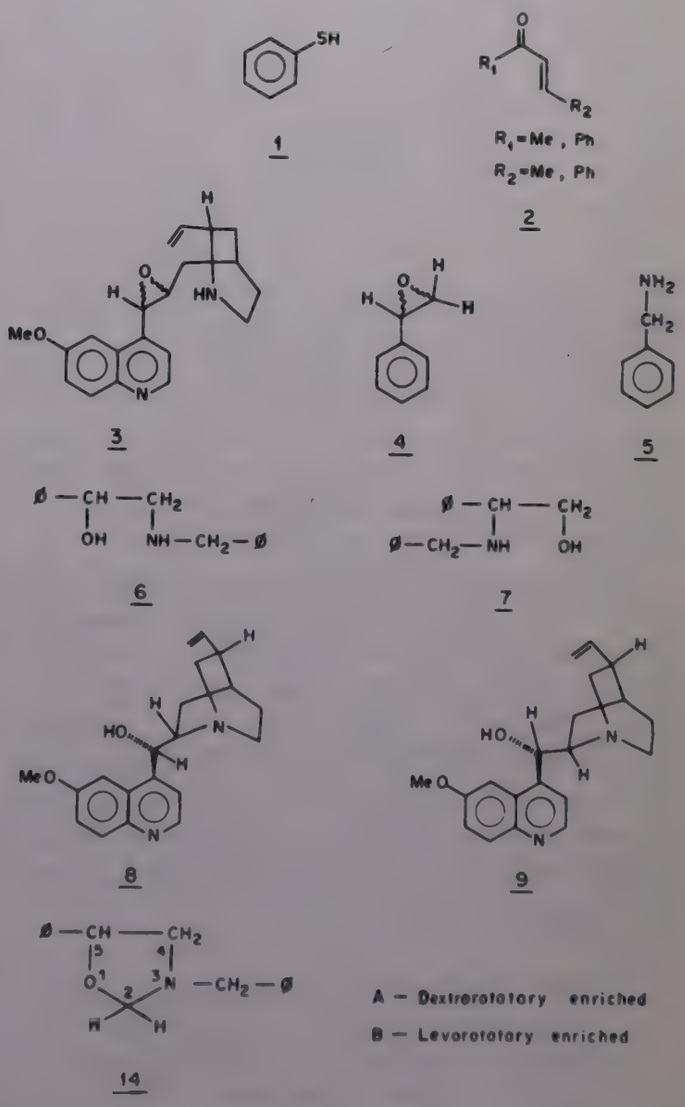
Interaction between phenyloxirane (**4**) and benzylamine (**5**) in the presence of quinine (**8**) and quinidine (**9**) and homogeneous catalysts, based on them, results in the formation of α-phenyl-β-benzylaminoethanol (**6**) exclusively and enriched with one of the optical enantiomers. The optical purity of **6** has been determined by specially devised technique based on ^{13}C NMR spectroscopy.

While investigating the mechanism of optical induction, catalysed by cinchona derivatives, during the Michael addition of thiophenol (**1**) to α, β-unsaturated ketones (**2**), intermediacy of a quinoline derivative such as **3** was envisaged[1,2]. To further substantiate the mechanism, we believe that a stuty of the oxirane ring-opening by various nucleophiles, under the influence of cinchona catalysts would be important. If the regioselectivity and stereoselectivity in these reactions could be controlled, it would lead to the synthesis of a number of biologically active compounds such as sympathomimetic drugs in economically feasible manner.

To start with, *dl*-phenyloxirane (**4**) was chosen as a substrate model, so that only one optical centre would be produced and further complications due to the formation of diastereoisomers would be avoided. The nucleophile chosen was benzylamine (**5**), which is virtually at the bottom of the nucleophilicity scale. This particular reaction was studied earlier by Browne[3] and Parkar[4,5] and was known to give α-phenyl-β-benzylaminoethanol (**6**) and β-phenyl-β-benzylaminoethanol (**7**) under different reaction parameters such as solvent, temperature, acid and basic reaction media.

Interaction between **4** and **5** in benzene in the presence of catalylic amount of quinine (**8**) and quinidine (**9**) led to the exclusive formation of **6** in good yield. The degree of optical induction was however low. Quinine catalysed reactions afforded **6**, in which dextrorotatory enantiomer predominated. On the other hand, in quinidine catalysed reactions, the product (**6**) was found to be enriched in levorotatory enantiomer.

It was found that the use of homogeneous catalysts‡ based on acetylacetonatomolybdenum oxide and quinine (Qn)/quinidine (Qd) such as [$QnMoO_2$(acac)] (**10**) and [$QdMoO_2$(acac)] (**11**) as well as the ones based on chloro-tris (triphenylphosphine) copper and quinine [$(PPh_3)_2Qn_2$]CuCl (**12**) and quinidine [$(PPh_3)_2Qd_2$]CuCl (**13**) could be advantageously used to increase optical yields[6,7]. The use of these catalysts, in very small quantities (to the extent of 10^{-6} g/gmol of



†NCL Communication No. 3934.

‡Detailed structural studies **10**, **11**, **12** and **13** are in progress.

reactants) did increase optical yields. As expected, the use of **10** yielded **6** enriched in dextrorotatory enantiomer and that of **11** afforded **6** enriched in levorotatory enantiomer. But the use of either **12** or **13** yielded levorotatory enriched enantiomer only. The optical yields were also better when **12** and **13** were used. (For comparison see Table 1).

Though in each case, a number of experiments were carried out to arrive at the optimum optical yields, only a few representative ones are mentioned in Table 1.

Two interesting observations were made during the course of this work. (i) All the reactions were carried out at room temperature for a prolonged period of about 220 hr. Higher temperature enhanced the rate of these reactions, but the extent of optical induction got reduced considerably. (ii) In none of the reactions, even if stopped prematurely, recovered phenyloxirane showed any rotation. This indicated that there was no kinetic resolution of phenyloxirane. It is quite likely that only one of the enantiomer of phenyloxirane gets resolved but the racemisation process sets in immediately under the reaction conditions. Racemisation of oxirane under basic or acidic conditions has been recorded in the literature[8], but under near neutral conditions, to our knowledge, is not known. It is quite likely that we are considering the phenomenon of racemisation by considering the classical structure of phenyloxirane and the known regio-steric factors which govern its opening. Dewar model of three-membered rings and his explanation of their reactivity may offer a clue to the above phenomena[9].

There are a number of β-amino alcohols whose optical purity is yet to be determined. Compound **(6)** is one such aminoalcohol. Most of the conventional methods, i.e. PMR with CLSR, PMR of derivatives with CLSR and ^{13}C NMR with CLSR, to determine optical purity fail in these compounds. A new method, devised by us[10], makes use of ^{13}C NMR spectroscopy of the derivatives of β-aminoalcohol, such as oxazolidines, in conjunction with chiral lanthanide shift reagent, Eu(hfc)$_3$.

Table 1 —Interaction of Phenyloxirane (**4**) and Benzylamine (**5**) in Presence of Different Catalysts: Formation of **6** Enriched in One of Optical Enantiomers

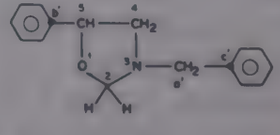
No	Catalyst	Cat quantity mg (gmol) gmol reactants	Specific rotation	Enantiomeric excess, %
1	**8**	41.6	+2.24	2.7
2	**9**	41.6	2.05	2.4
3	**10**	10.4	+5.52	6.8
4	**11**	10.4	−4.93	5.7
5	**12**	20.2	−6.38	7.5
6	**13**	20.2	−9.77	11.6

For determining the optical purity of the compounds in the present work, the above strategy was successfully employed. Thus oxazolidine derivative of **6** (DL, dextrorotatory enriched and levorotatory enriched) were prepared by conventional method[11]. Carbon-13 spectrum of DL-3-benzyl-5-phenyl-oxazolidine (**14**) prepared from **6** was scanned and carbon line assignments were done on the basis of off resonance technique and carbon-proton coupled spectra. This spectrum was rescanned on adding Eu(hfc)$_3$. The best separation of carbon lines due to 'D' and 'L' enantiomers was achieved when Eu(hfc)$_3$ concentration reached about 50% wt/wt. (Tables 2 and 3 for chemical shifts).

The dextrorotatory enriched compound (entry 3, Table 1) was converted into its oxazolidine derivative (**14A**) $[\alpha]_D^{25} = +8.14]$. Its ^{13}C spectrum was scanned in the presence of Eu(hfc)$_3$ (50% wt/wt). Carbon lines due to C-2 were best resolved (down to the base). The intensity ratios of these lines showed that the % of dextrorotatory isomer was 53.4 and that of levorotatory isomer was 46.6 (Table 2). As the yield of oxazolidine derivative (**14A**) was quantitative, it was assumed that this enantiomeric composition represented the one in the starting dextrorotatory enriched compound. Back computation of this and other results indicated that the specific rotation of pure dextrorotatory enantiomer of **6** would be +80.0.

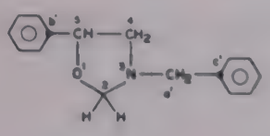
Similar ^{13}C studies were carried out on the oxazolidine derivative (**14B**) $[\alpha_D^{25} = -6.9]$ prepared from **6**, enriched in levorotatory enantiomer (entry 4, Table 1). Reversal of intensities was observed for carbon lines for D and L isomers. Again carbon lines

Table 2 —Carbon-13 NMR Signals in Oxazolidine Derivative (**14A**)



Carbon with increasing chemical shift	Signal (δ)	Shift (ppm) with CLSR	$\Delta\delta$ (ppm)		Integral intensity ratio
C-4	58.282	59.272	0.990	0.273	50.69
		59.545	1.263		49.31
C-a'	60.517	61.450	0.933	–	
C-5	76.468	77.969	1.501	0.660	54.26
		78.629	2.161		45.74
C-2	87.384	89.756	1.372	1.052	53.41
		90.808	2.424		46.59
C-c'	138.408	138.701	0.293	0.100	49.50
		138.801	0.393		50.50
C-b'	141.888	142.666	0.778	0.448	51.83
		143.114	1.226		48.17

Table 3—Carbon-13 NMR Signals in Oxazolidine Derivative (**14B**)



Carbon with increasing chemical shift	Signal (δ)	Shift (ppm) with CLSR	$\Delta\delta$ (ppm)		Integral intensity ratio
C-4	58.241	59.175	0.934	0.297	47.19
		59.472	1.231		52.81
C-a′	60.498	61.364	0.856	—	—
C-5	76.450	77.832	1.382	0.604	51.56
		78.436	1.986		48.44
C-2	87.362	89.563	2.201	0.971	47.15
		90.534	3,172		52.85
C-c′	138.408	138.682	0.174	—	—
C-b′	141.907	—	—	—	—

due to C-2 were best resolved and the difference showed the excess of L isomer to the extent of 5.7% (Table 3). The specific rotation of pure levorotatory enantiomer of **6**, thus works out to be −85.0°. In most cases, the dextro- and levo-rotatory isomers show equal and opposite rotation. The above values indicate the accuracy of our results, and the validity of the ^{13}C method developed by us[10], of course, within the experimental error.

This work has, no doubt, proved the potentiality of the homogeneous catalysts based on quinine and quinidine in nucleophillic opening of oxirane rings. Other factors governing the regiospecificity and stereoselectivity in this ring-opening are under investigation.

Experimental Procedure

Carbon-13 FT NMR (proton noise decoupled) spectra were recorded on a JOEL-FX-100 spectrometer, operating at 25.05 MHz and equipped with JOEL-980 computer. The spectra were recorded in $CDCl_3$. Commercially available tris-[(3-heptafluoropropylhydroxymethylene) *d*-camphoroto] europium (III) [$Eu(hfc)_3$], quinine, quinidine and benzylamine were used. Catalysts **10**, **11**, **12** and **13** were synthesised in our laboratory[7].

General procedure for interaction between benzylamine (**5**) *and dl-phenyloxirane* (**4**)

Equimolar quantities (generally 0.01 mol) of **5** and **4** and appropriate catalyst (for representative quantities refer to Table 1) were dissolved in benzene and the resulting mixture was stirred at room temperature for 220-240 hr. Benzene was evaporated and the residual oil was subjected to fractional distillation. Unreacted **4** and **5** were distilled out at 60-70°/2.0 mm. The product **6** then distilled at 100-10°/0.003 mm; yield 85%; IR: 3400 cm^{-1} (NH, OH-broad); PMR: 2.75 [*m*, 5H; O*H*, NH_2 (partially exchangeable with D_2O) and CH-CH_2), 3.8 (*s*, 2H, N-CH_2], 3.8 (*s*, 2H, N-CH_2-C_6H_5), 4.68 (*dd*, 1H, C*H*-CH_2), 7.1 (10H, aromatic). (Found: C, 79.1; H, 6.7. $C_{15}H_{17}NO$ requires C, 79.3; H, 6.6%).

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Synthesis of a Triazolophenanthridine via Photocyclization of 3,4-Diaryl-5-hydroxy-Δ^2-1,2,4-triazoles

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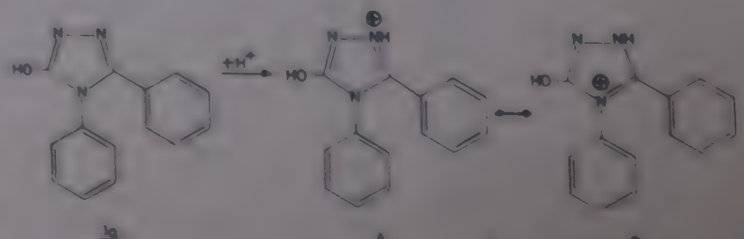
The oxidative and eliminative 1,6-photocyclization of 4,5-diphenyl-3-hydroxy-Δ^2-1,2,4-triazole (**1a**) and derivatives containing bromine in *ortho*-position in either of the two phenyl groups (**1b** and **1c**) gives the *s*-triazolo[4,3-*f*]phenanthridine (**5**). Compound (**1a**) is oxygen-sensitive under photoexcitation. Irradiation of protonated **1a** in the presence of oxygen gives benzanilide probably via *endo*-peroxide formation followed by loss of nitrogen and carbon dioxide. If oxygen is excluded the protonated species of **1a** capable of exhibiting amidine resonance, provides a heterotriene system for photochemical 6π-electron ring closure.

The 6π-electron photochemical electrocyclic ring closure of *cis*-stilbene followed by oxidation to give phenanthrene has prompted the extension and application of this reaction for the synthesis of various carbo and heterocyclic ring systems[1]. In general, a formal homo or heterotriene system must be present to allow photocyclization[1,2]. Diaryl amines, ethers, sulfides and selenides which are considered as isoelectronic with the pentadienyl anion undergo 1,5-cyclization to give the corresponding pyrrole, furan, thiophene and selenophene derivatives[3]. Although a formal triene system is absent in benzanilide, this compound photocyclizes to give phenanthridone[4]. Photocyclization where the amide function is replaced by an amidine function has not been investigated. We were prompted to carry out one such photocyclization as one of us observed cyclization in the mass spectral studies of 3,4-diphenyltriazole derivatives[5]. These compounds gave an abundant M−1 mass peak. Mechanistically this was shown to arise from cyclization leading to the heterofused triazolophenanthridine derivative. Quite often there exists a parallel between some reactions observed under electron impact and photochemical conditions[6]. Our choice, therefore, fell on 5-hydroxy-3,4-diphenyl-Δ^2-1,2,4-triazole (**1a**). The two phenyl rings in **1a** are in vicinal positions to an amidine function incorporated in the ring so that the two aryl groups are in appropriate configuration to facilitate photocyclization. Compounds of type **1** are easily accessible by oxidative cyclization[7] with alkaline hexacyanoferrate (III) of 4-aryl semicarbazones of aromatic aldehydes.

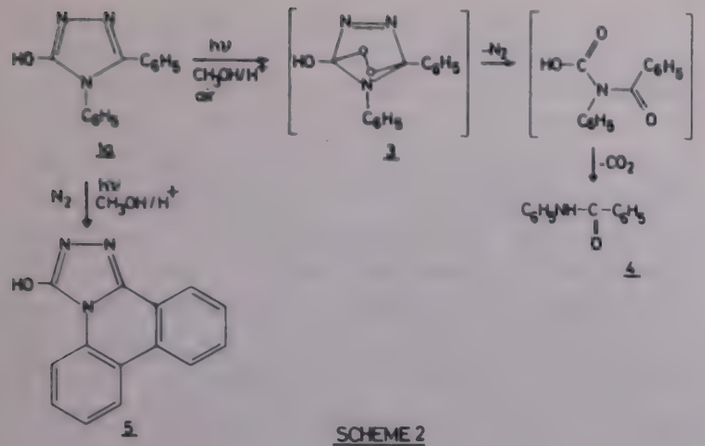
Our first attempt was to obtain the cyclized product by direct irradiation of **1a** in methanol or acetonitrile (0.01 *M* solution) at 2537 A°. No change took place in **1a** even after several hours of irradiation (TLC monitoring). An identical result was obtained even in the presence of iodine. Irradiation under a stream of air led to the very slow disappearance of starting **1a** and formation of aniline and benzoic acid along with traces of three other products which were not characterized. The presence of aniline and benzoic acid in the reaction mixture was shown by co-injection GC analysis.

The compound 3-hydroxy-Δ^2-1,2,4-triazole has earlier been shown to exist exclusively in the lactim form in solution[8]. Compound (**1a**) can also be expected to be present in the lactim form in solution. A formal heterotriene system is not present in **1a** to facilitate electrocyclic ring closure. However, we reasoned that in acidic medium, protonation of nitrogen in the second position can set in an amidine resonance between canonical forms **2A** and **2B** as shown in Scheme 1. This might result in photocyclization.

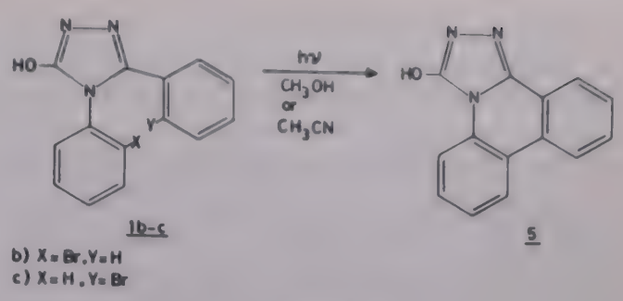
However, irradiation of **1a** in methanol in the presence of sulphuric acid at 2537 Å in a stream of air gave benzanilide as the major product, besides trace amounts of two other compounds that could not be isolated by column chromatography. No cyclized product was detected on TLC. That compound **1a** was thermally stable under identical conditions, was shown in a separate experiment, which involved refluxing it in methanol in the presence of sulphuric acid in a stream



SCHEME 1



SCHEME 2



SCHEME 3

of air. The photooxygenation[9] of heterocyclic compounds to give an *endo*-peroxide via (4 + 2)cycloaddition or dioxetane-type of compounds via (2 + 2)cycloaddition across carbon terminals is known, but only in the presence of a sensitizer to generate singlet oxygen. Though the photochemical cleavage of **1a** in acidic medium in the presence of air to give benzanilide can be explained by assuming a priori formation of an *endo*-peroxide (**3**) followed by successive elimination of nitrogen and carbon dioxide (see Scheme 2), the absence of a sensitizer excludes the involvement of singlet oxygen unless **1a** itself acts as a sensitizer. This needs further verification.

Compound (**1a**), when irradiated in methanol in the presence of sulphuric acid at 2537 Å under constant nitrogen blanket, gave a TLC single product which could be isolated by column chromatography. The UV, IR and mass spectra of this compound were superimposable with those of an authentic sample of 3-hydroxy-*s*-triazolo[4,3-*f*]phenanthridine (**5**) prepared by an independent synthesis[10] reported more than two decades ago starting from 3-(2-aminophenyl)-5-hydroxy-4-phenyl-Δ^2-1,2,4-triazole and more recently[11] from phenanthridone through α-hydrazinophenanthridine. Qualitatively the photocyclization of **1a** in methanol in the presence of an acid under exclusion of oxygen proceeded slowly. We expected that the presence of a halogen substituent in *ortho* position in any one of the two phenyl rings might facilitate photocyclization, as was observed in the case of 3-(2-chlorophenyl)-2,5-diphenyl-Δ^2-1,2,4-triazole and other haloaryl containing heterocycles[12]. We, therefore, prepared two new compounds **1b** and **1c** by the known method[7]. Irradiation of **1b** or **1c** at 2537 Å or 3000 A° in nondeaerated solutions in methanol or acetonitrile gave the cyclized product **5** (Scheme 3) in good yields. The product separated in crystalline form and needed no further purification.

It is thus clear that 5-hydroxy-3,5-diphenyl-Δ^2-1,2,4-triazole (**1a**) and similar derivatives having a bromine substituent in *ortho* position in any one of the vicinal phenyl rings as in **1b** or **1c** undergo photocyclization. The parent **1a** probably undergoes 6π-electron ring closure in acidic medium if oxygen is excluded. There are two mechanistic possibilities for the cyclization of the bromo derivative **1b** or **1c** both of which do not involve electrocyclic ring closure. The eliminative cyclization of **1b** or **1c** may proceed either by radical ion formation through electron transfer reaction or by homolytic cleavage of the halogen atom. A recent work[12] has been interpreted in favour of homolytic cleavage of halogen, helped by complex formation from S_0^v state. Since both the components borne on the carbon and nitrogen can be varied widely, we believe that the method described here will be very useful for the synthesis of other tricyclic heterocycles also.

Experimental Procedure

All irradiations were carried out in quartz tubes in a Srinivasan-Rayonet photochemical reactor fitted with 16 lamps with a cooling fan on. Mass spectra were recorded on a VG micromass 7070H unit. Silica gel (Acme, 200 mesh) and plates coated with silica gel-G (nach Stahl) were used for column and TLC, respectively. The gas chromatographic analysis was carried out on HP 5880 model using FID detector on a 8″ × 1/8″ column packed with 5% OV-17 on chromosorb WHP (80-100 mesh).

5-Hydroxy-3,5-diphenyl-Δ^2-1,2,4-triazole (**1a**) was prepared from aniline and nitrourea in four steps following a reported procedure[7].

4-(2-Bromophenyl)-5-hydroxy-3-phenyl-Δ^2*-1,2,4-triazole* (**1b**):

(a) N-(2-bromophenyl)urea

The urea was prepared by adding a saturated aq solution of nitrourea (5 g; 0.046 mol) to 2-bromoaniline (8 g; 0.046 mol) maintained at 80°. The effervescence rate was controlled by alternate heating and cooling till the nitrourea addition was complete. After allowing the reaction mixture to stand for 48 hr at room temperature, the solid was filtered, washed with dil acetic acid and recrystallized from ethanol, m.p. 198° (reported[13], m.p. 202°), 8.7 g (87%).

(b) 4-(2-Bromophenyl)semicarbazide[14]

A mixture of N-(2-bromophenyl)-urea (6 g, 0.026 mol), hydrazine hydrate (5 ml) in absolute ethanol (3 ml) was kept under slow reflux for 8 hr. After decolourisation with charcoal, the reaction mixture was filtered and washed with warm water (2 × 10 ml). The combined filtrate on cooling gave a crystalline product which was further purified by recrystallization from ethanol, m.p. 128-29°; 5.3 g (83%); MS: M^+ at *m/z* 229 and isotope peak at *m/z* 231.

(c) 1-Benzal-4-(2-bromophenyl)semicarbazone

A solution of 4-(2-bromophenyl)-semicarbazide (4 g; 0.125 mol) and benzaldehyde (1.27 g; 0.012 mol) in ethanol was refluxed for 90 min, cooled, diluted with chilled water, filtered and the solid recrystallized from ethanol, m.p. 195°; 4.8 g (87%); MS: M^+ at *m/z* 317 and isotope peak at *m/z* 319.

(d) 4-(2-Bromophenyl)-5-hydroxy-3-phenyl-Δ^2*-1,2,4-triazole* (**1b**)

Oxidative cyclisation of the above semicarbazone as per described procedure[7] gave **1b** which recrystallized from methanol, m.p. 231-32°; 70% yield; MS: M^+ *m/z* 315.0007 (M^+; high resolution); calculated for $C_{14}H_{10}{}^{79}Br\,N_3O$: 315.0007.

3-(2-Bromophenyl)-5-hydroxy-4-phenyl-Δ^2*-1,2,4-triazole* (**1c**):

(a) 1-(2-Bromobenzal)-4-phenylsemicarbazone

A solution of 4-phenylsemicarbazide (2 g, 0.013 mol) and *o*-bromobenzaldehyde (1.4 g, 0.0075 mol) in ethanol was refluxed for 25 min, cooled, diluted with chilled water, filtered and dried, m.p. 200°; 3.8 g (90%); MS: M^+ at *m/z* 317 and isotope peak at *m/z* 319.

(b) The oxidative cyclisation of this semicarbazone to **1c** was carried out in ethanolic sodium hydroxide, using potassium hexacyanoferrate (III) as described in literature[7]. The product was recrystallized from ethanol, m.p. 186°; 66% yield; MS: *m/z* 316.9987 (M^+; high resolution); calculated for $C_{14}H_{10}{}^{81}Br\,N_3O$: 316.9994.

Irradiation of 5-hydroxy-3,4-diphenyl-Δ^2*-1,2,4-triazole* (**1a**):

(a) In acid medium in presence of air

A drop of sulphuric acid was added to a solution (20 ml) of **1a** (0.01 mol) in methanol. This solution was irradiated at 2537 Å, while passing a stream of air. After irradiation for 4 hr, the solvent was removed and the mixture chromatographed over silica gel (eluant chloroform). Benzanilide eluted first followed by the unreacted **1a**.

(b) Irradiation in acidic medium in nitrogen atmosphere

A solution (20 ml) of **1a** (0.01 mol) in methanol was acidified with a drop of sulphuric acid and irradiated at 2537 Å for 28 hr with continued purging with nitrogen. The mixture was concentrated to approximately half of its volume and the hydroxytriazolophenanthridine (**5**) which separated was filtered, washed with methanol and dried *in vacuo*, m.p. 290° (d), 16.4 mg; (35%). A mixed m.p. determination with an authentic specimen, prepared by either of the methods[10,11] indicated no depression. The IR spectrum of the photochemically prepared product was also superimposable with that of the authentic specimen. The unreacted **1a** present in the filtrate was recovered by passing over silica gel column and eluting with chloroform.

Irradiation of 4-(2-bromophenyl)-5-hydroxy-3-phenyl-Δ^2*-1,2,4-triazole* (**1b**)

A solution (23 ml) of **1b** (0.016 mol) in acetonitrile was irradiated at 2537 Å. After 1.5 hr the hydroxytriazolophenanthridine (**5**) that separated was filtered, washed with methanol and dried *in vacuo*, yield 69 mg (77%).

Irradiation of 3-(2-bromophenyl)-5-hydroxy-4-phenyl-Δ^2*-1,2,4-triazole* (**1c**)

A solution (23 ml) of **1c** (0.016 mol) in acetonitrile was irradiated at 2537 Å for 1.5 hr. The hydroxytriazolophenanthridine (**5**) was isolated as described above, yield 48 mg (53%).

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Synthesis of Isomeric Δ^2-Pyrazolines

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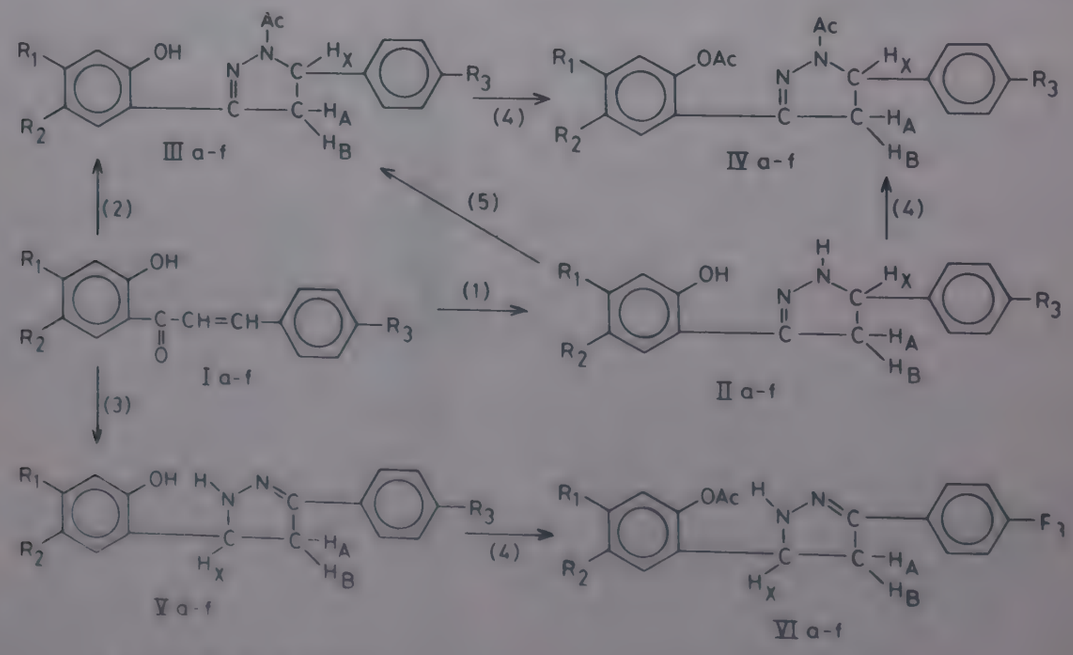
2'-Hydroxychalkones (I) react with hydrazine hydrate in ethanol to give 5-aryl-3-(2-hydroxyphenyl)-Δ^2-pyrazolines (II) while in acetic acid the corresponding 5-aryl-1-acetyl-3-(2-hydroxyphenyl)-Δ^2-pyrazolines (III) are obtained contrary to the reported isomerisation of pyrazolines (II) in acetic acid. Acetylation of both II and III gives 5-aryl-1-acetyl-3-(2-acetoxyphenyl)-Δ^2-pyrazolines (IV). However, chalkones I react with hydrazine hydrochloride in DMF to give the isomeric 3-aryl-5-(2-hydroxyphenyl)-Δ^2-pyrazolines (V) which on acetylation afford 3-aryl-5-(2-acetoxyphenyl)-Δ^2-pyrazolines (VI).

Mustafa *et al.*[1] have reported that 5-arylacryloyl-6-hydroxy-4,7-dimethoxy-benzo[*b*]furans react with hydrazine hydrate in ethanol to give hydrazones which on boiling with acetic acid yield the corresponding pyrazolines. In a later study by Aziz *et al.*[2] the reaction between hydrazine hydrate and 5-arylacryloyl-6-methoxy-benzo[*b*]furans was shown to yield the corresponding Δ^2-pyrazolines via 1,4-addition in ethanol and the isomeric Δ^2-pyrazolines via 1,2-addition in acetic acid. The isomerisation of 1,4-addition product to 1,2-addition product in boiling acetic acid was also reported by these workers[2]. This prompted us to report our results on the reaction of 2'-hydroxychalkones (I) with hydrazine hydrate in ethanol and acetic acid.

The reaction of 2'-hydroxychalkones (Ia-f) with hydrazine hydrate in ethanol did not give the reported[1] chalkone hydrazones but the products were identified as 5-aryl-3-(2-hydroxyphenyl)-Δ^2-pyrazolines (IIa-f). The structures (IIa-f) assigned to the products were based on the identity of IIf with an authentic sample[3]. The formation of IIa-f is possible only by 1,2-addition.

On boiling in acetic acid IIa-f did not undergo isomerisation as reported earlier but instead afforded[4] 5-aryl-1-acetyl-3-(2-hydroxyphenyl)-Δ^2-pyrazolines (IIIa-f). The IR spectra of IIIa was devoid of a strong



Scheme 1

band at 3320 (NH of substituted pyrazoline) but exhibited a band at 1660 cm^{-1} due to N-acetyl function.

Acetylation of IIa-f or IIIa-f with Ac_2O-NaOAc yielded 5-aryl-1-acetyl-3-(2-acetoxyphenyl)-Δ^2-pyrazolines (IVa-f). The IR spectrum of IVa was devoid of a band at 3120 (OH) but displayed two bands at 1660 and 1750 cm^{-1} due to $N-COCH_3$ and $-O-COCH_3$ functions respectively. The PMR spectrum of IVa exhibiting a six proton singlet at δ 2.3 due to two $-COCH_3$ functions also supported the proposed structure.

It is well known that the formation of pyrazoline from 2'-hydroxychalkones and hydrazine is governed by a number of factors such as *p*H, temperature and the solvent. This prompted us to study the reaction between 2'-hydroxychalkone and hydrazine hydrochloride in ethanol alone or in the presence of aq. sodium acetate or NaOH or in DMF.

The reaction products of Ia-f with hydrazine hydrate in DMF[5] or hydrazine hydrochloride and aq. AcONa or NaOH in ethanol were similar to IIa-f and not the corresponding isomer of IIa-f. Further, Ia-f failed to react with hydrazine hydrochloride in ethanol alone even on prolonged refluxing (6 to 8 hr). On the other hand, Ia-f reacted with hydrazine hydrochloride in DMF (soft base) to give Va-f which remained unchanged on prolonged boiling in acetic acid. This suggest that Va-f are not chalkone hydrazones since chalkone hydrazones on boiling in acetic acid give pyrazolines[1]. As the product obtained from If and hydrazine hydrochloride was not found to be identical with IIf, it must have the isomeric structure (Vf).

The failure to obtain 3-aryl-1-acetyl-5-(2-hydroxyphenyl)-Δ^2-pyrazoline by refluxing in acetic acid may be attributed to the presence of strong H-bond between O-atom of hydroxy group and H-atom of NH group of pyrazoline ring.

Acetylation of 3-aryl-5-(2-hydroxyphenyl)-Δ^2-pyrazolines (Va-f) with Ac_2O-NaOAc gave 3-aryl-5-(2-acetoxyphenyl)-Δ^2-pyrazolines (VIa-f) leaving the NH group in pyrazoline intact. The absence of a band at 3040 (OH) and appearance of bands at 2940 (NH of pyrazoline) and 1750 cm^{-1} ($O-COCH_3$) in the IR spectrum of VIa supported the proposed structure.

Experimental Procedure

Melting points reported are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer 577 spectrophotometer (ν_{max} in cm^{-1}), UV spectra in MeOH on a Perkin-Elmer 202 spectrophotometer (λ_{max} in nm), and 90 MHz PMR spectra in $CDCl_3$ on a Perkin-Elmer R-32 instrument using TMS as internal standard (chemical shifts in δ, ppm).

2'-Hydroxychalkones (Ia-f) were prepared by literature method[6].

5-Anisyl-3-(2-hydroxy-5-methylphenyl)-Δ^2-pyrazoline (IIa)

A mixture of 2'-hydroxy-4-methoxy-5'-methylchalkone (Ia, 2.68 g, 0.01 mol), ethanol (20 ml) and hydrazine hydrate (1 ml, 0.02 mol) was heated under reflux for 2 hr. The product thus seperated was worked-up as usual and crystallised from ethanol to get IIa, m.p. 113°, yield 2.0 g (71%) (Found: C, 72.1; H, 6.2; N, 9.6. $C_{17}H_{18}O_2N_2$ requires C, 72.3; H, 6.4; N, 9.9%); IR (KBr): 3320 (NH), 2950-3000 (bonded OH) and 1590-1600 (C = N)[7]; UV (MeOH): 220, 280 and 320; PMR ($CDCl_3$): 2.20 (*s*, 3H, CH_3), 2.99 (*dd*, 1H, H_A, $J_{AB} = 18$, $J_{AX} = 5$ Hz), 3.39 (*dd*, 1H, H_B, $J_{AB} = 18$, $J_{BX} = 11$ Hz), 3.7 (*s*, 3H, OCH_3), 4.7 (*t*, 1H, H_X, $J_{AX} = 5$, $J_{BX} = 11$ Hz), 5.8-5.9 (*s*, 1H, NH), 6.7-7.3 (*m*, 7H, Ar-*H*).

Following members of the series were also prepared in a similar way.

IIb: Low melting, yield 64% (Found: C, 76.0; H, 6.2; N, 10.9. $C_{16}H_{16}ON_2$ requires C, 76.2; H, 6.3; N, 11.1%).

IIc: m.p. 139°, yield 70% (Found: C, 72.1; H, 6.2; N, 9.7. $C_{17}H_{18}O_2N_2$ requires C, 72.3; H, 6.4; N, 9.9%).

IId: m.p. 167°, yield 70% (Found: C, 76.0; H, 6.2; N, 10.9. $C_{16}H_{16}ON_2$ requires C, 76.2; H, 6.3; N, 11.1%).

IIe: m.p. 103°, yield 67% (Found: C, 71.4; H, 5.8; N, 10.3. $C_{16}H_{16}O_2N_2$ requires C, 71.6; H, 6.0; N, 10.4%).

IIf: m.p. 88°, (lit.[3], m.p. 88-89.5°), yield 68% (Found: C, 75.5; H, 5.7; N, 11.7. $C_{15}H_{14}ON_2$ requires C, 75.6; H, 5.9; N, 11.8%).

1-Acetyl-5-anisyl-3-(2-hydroxy-5-methylphenyl)-Δ^2-pyrazoline (IIIa)

(a) A mixture of IIa (1.41 g, 0.005 mol) and acetic acid (10 ml) was heated under reflux for 2 hr and diluted with water. The product thus seperated was filtered and crystallised from ethanol to get IIIa, m.p. 176°, yield 1.15 g (70%) (Found: C, 70.2; H, 6.1; N, 8.6. $C_{19}H_{20}O_3N_2$ requires C, 70.4; H, 6.2; N, 8.6%); IR (KBr): 3120 (OH), 1660 ($N-COCH_3$), 1590-1600 (C = N of pyrazoline); UV (MeOH): 220, 280 and 330; PMR ($CDCl_3$): 2.2 (*s*, 3H, CH_3), 2.3 (*s*, 3H, $COCH_3$), 3.21 (*dd*, 1H, H_A, $J_{AB} = 18$, $J_{AX} = 5$ Hz), 3.7 (*s*, 3H, OCH_3), 3.71 (*dd*, 1H, H_B, $J_{AB} = 18$, $J_{BX} = 11$ Hz), 5.41 (*dd*, 1H, H_X, $J_{AX} = 5$, $J_{BX} = 11$ Hz), 6.7-7.2 (*m*, 7H, Ar-*H*), 10.0 (*s*, 1H, OH).

Following members of the series were also prepared in a similar manner.

IIIb: m.p. 142°, yield 65% (Found: C, 73.3; H, 6.0; N, 9.5. $C_{18}H_{18}O_2N_2$ requires C, 73.8; H, 6.1; N, 9.5%).

IIIc: m.p. 153°, yield 69% (Found: C, 70.2; H, 6.0; N, 8.5. $C_{19}H_{20}O_3N_2$ requires C, 70.4; H, 6.2; N, 8.6%).

IIId: m.p. 175°, yield 65% (Found: C, 73.3; H, 6.0; N, 9.5. $C_{18}H_{18}O_2N_2$ requires C, 73.5; H, 6.1. N, 9.5%).

IIIe: m.p. 143°, yield 71% (Found: C, 69.5; H, 5.7; N, 8.9. $C_{18}H_{18}O_3N_2$ requires C, 69.7; H, 5.8; N, 9.0%).

IIIf: m.p. 142°, (lit.[3], m.p. 136-138°), yield 70% (Found: C, 72.7; H, 5.6; N, 9.9. $C_{17}H_{16}O_2N_2$ requires C, 72.8; H, 5.7; N, 10%).

(b) A mixture of I (0.01 mol), acetic acid (20 ml) and hydrazine hydrate (0.02 mol) was refluxed for 2 hr, and diluted with excess of water. Usual work-up and crystallisation of the product from ethanol gave III in 65-70% yield, m.p. remained undepressed on admixture with the samples obtained in (a).

1-Acetyl-3-(2-acetoxy-5-methylphenyl)-5-anisyl-Δ^2-pyrazoline (IVa)

A mixture of IIIa (0.5 g) acetic anhydride (3 ml) and a pinch of fused sodium acetate was heated under reflux for 45 min and was diluted with water. The solid thus obtained was crystallised from ethanol to get IVa, m.p. 127°, yield 0.4 g (71%) (Found: C, 68.6; H, 5.9; N, 7.5. $C_{21}H_{22}O_4N_2$ requires C, 68.6; H, 6.0; N, 7.6%); IR (KBr): 1750 ($O-COCH_3$), 1660 ($N-COCH_3$), 1600 (C = N); UV (MeOH): 230 and 290; PMR ($CDCl_3$): 2.2 (*s*, 3H, CH_3), 2.3 (*s*, 6H, $2\times COCH_3$), 3.08 (*dd*, 1H, H_A, $J_{AB}=18$, $J_{AX}=5$ Hz), 3.64 (*dd*, 1H, H_B, $J_{AB}=18$, $J_{BX}=11$ Hz), 3.7 (*s*, 3H, OCH_3), 5.37 (*dd*, 1H, H_X, $J_{AX}=5$, $J_{BX}=11$ Hz), 6.7-7.4 (*m*, 7H, Ar-*H*).

Other acetyl derivatives of the type IV were prepared in a similar manner and their characterization data are given below:

IVb: m.p.157°, yield 67% (Found: C, 71.2; H, 5.8; N, 8.3. $C_{20}H_{20}O_3N_2$ requires C, 71.4; H, 5.9; N, 8.3%).

IVc: m.p. 107°, yield 65% (Found: C, 68.6; H, 5.9; N, 7.6. $C_{21}H_{22}O_4N_2$ requires C, 68.8; H, 6.0; N, 7.6%).

IVd: m.p. 139°, yield 63% (Found: C, 71.2; H, 5.8; N, 8.2. $C_{20}H_{20}O_3N_2$ requires C, 71.4; H, 5.9; N, 8.3%).

IVe: m.p. 95°, yield 65% (Found: C, 68.0; H, 5.7; N, 7.9. $C_{20}H_{20}O_4N_2$ requires C, 68.2; H, 5.8; N, 7.9%).

IVf: m.p. 149° (lit.[3], m.p. 147-49°), yield 64% (Found: C, 70.6; H, 5.4; N, 8.5. $C_{19}H_{18}O_3N_2$ requires C, 70.8; H, 5.6; N, 8.7%).

The compounds IVa-f could also be obtained directly by the acetylation of 5-aryl-3-(2-hydroxyphenyl)-Δ^2-pyrazolines (IIa-f) with acetic anhydride and fused sodium acetate in about 65% yield.

3-Anisyl-5-(2-hydroxy-5-methylphenyl)-Δ^2-pyrazoline (Va)

Chalkone Ia (2.68 g, 0.01 mol), and hydrazine hydrochloride (2.1 g, 0.02 mol) were refluxed in DMF for 2 hr. The reaction mixture on cooling was diluted with water, and the product seperated was filtered and crystallised from ethanol-acetic acid to get Va, m.p. 165°, yield 1.7 g (63%) (Found: C, 72.2; H, 6.2; N, 9.7. $C_{17}H_{18}O_2N_2$ requires C, 72.3; H, 6.4; N, 9.9%); IR (KBr) 3040 (OH), 2920 (NH), 1670 (C = N)[7]; UV (MeOH): 220, 280 and 330; PMR ($CDCl_3$): 2.2 (*s*, 3H, CH_3), 3.25 (*dd*, 1H, H_A, $J_{AB}=18$, $J_{AX}=5$ Hz), 3.7 (*s*, 3H, OCH_3), 3.72 (*dd*, 1H, H_B, $J_{AB}=18$, $J_{BX}=11$ Hz), 5.33 (*dd*, 1H, H_X, $J_{AX}=5$, $J_{BX}=11$ Hz), 6.7-7.2 (*m*, 7H, Ar-*H*), 8.8 (*s*, 1H, NH), 9.8 (*s*, 1H, OH).

The characterization data of other members of the series V, prepared in a similar way, are as follows:

Vb: m.p. 144°, yield 60% (Found: C, 76.0; H, 6.2; N, 10.9. $C_{16}H_{16}ON_2$ requires C, 76.2; H, 6.3; N, 11.1%).

Vc: m.p. 188°, yield 63% (Found: C, 72.1; H, 6.2; N, 9.8. $C_{17}H_{18}O_2N_2$ requires C, 72.3; H, 6.4; N, 9.9%).

Vd: m.p. 170°, yield 61% (Found: C, 76.1; H, 6.1; N, 11.0. $C_{16}H_{16}ON_2$ requires C, 76.2; H, 6.3; N, 11.1%).

Ve: m.p. 164°, yield 64% (Found: C, 71.5; H, 5.7; N, 10.3. $C_{16}H_{16}O_2N_2$ requires C, 71.6; H, 6.0; N, 10.4%).

Vf: m.p. 151°, yield 60% (Found: C, 75.4; H, 5.7; N, 11.6. $C_{15}H_{14}ON_2$ requires C, 75.6; H, 5.9; N, 11.8%).

5-(2-Acetoxy-5-methylphenyl-3-anisyl-Δ^2-pyrazoline (VIa)

Compound Va (0.5 g) was acetylated as described above to get VIa which was crystallised from ethanol, m.p. 167°, yield 0.35 g (70%) (Found: C, 70.2; H, 6.0; N, 8.5. $C_{19}H_{20}O_3N_2$ requires C, 70.4; H, 6.2; N, 8.6%); IR (KBr): 2900-2940 (NH), 1750 ($O-COCH_3$), 1660 (C = N of Δ^2-pyrazoline); UV (MeOH): 220 and 280; PMR ($CDCl_3$): 2.25 (*s*, 3H, CH_3), 2.3 (*s*, 3H, $COCH_3$), 3.16 (*dd*, 1H, H_A, $J_{AB}=18$, $J_{AX}=5$ Hz), 3.7 (*s*, 3H, OCH_3), 3.76 (*dd*, 1H, H_B, $J_{AB}=18$, $J_{BX}=1$ Hz), 5.32 (*dd*, 1H, H_X, $J_{AX}=5$, $J_{BX}=11$ Hz), 6.7-7.3 (*m*, 7H, Ar-*H*), 8.8 (*s*, 1H, NH).

Other members, prepared similarly, are as follows:

VIb: m.p. 151°, yield 68% (Found: C, 73.3; H, 6.0; N, 9.4. $C_{18}H_{18}O_2N_2$ requires C, 73.5; H, 6.1; N, 9.5%).

VIc: m.p. 126°, yield 71% (Found: C, 70.1; H, 6.0; N, 8.5. $C_{19}H_{20}O_3N_2$ requires C, 70.4; H, 6.2; N, 8.6%).

VId: m.p. 132°, yield 66% (Found: C, 73.3; H, 6.0; N, 9.4. $C_{18}H_{18}O_2N_2$ requires C, 73.5; H, 6.1; N, 9.5%).

VIe: m.p. 137°, yield 70% (Found: C, 69.5; H, 5.7; N, 8.9. $C_{18}H_{18}O_3N_2$ requires C, 69.7; H, 5.8; N, 9.0%).

VIf: m.p. 153°, yield 65% (Found: C, 72.7; H, 5.5; N, 9.9. $C_{17}H_{16}O_2N_2$ requires C, 72.8; H, 5.7; N, 10.0%).

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Enamines: Part III—A New Synthesis of Substituted 2-Arylisatogens & *o*-Nitrophenyl Benzyl Ketones†

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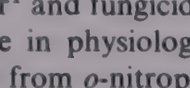
Condensation of substituted *o*-nitrobenzoyl chloride with *o*/*p*-nitro substituted β-morpholinostyrenes gives α-acyl-β-morpholinostyrenes which are converted into the title compounds.

2-Substituted isatogens are of current interest since they possess antitubercular[1] and fungicidal[2] activities and also play a vital role in physiology[3-5]. These isatogens can be obtained from *o*-nitrophenyl benzyl ketones (**4**) by cyclodehydration[6]. It seemed to us that synthesis of **4** by a new approach is worth exploring and an attractive candidate will be the enamines of substituted phenylacetaldehydes which on acylation with *o*-nitrobenzoyl chloride followed by hydrolysis and deformylation with acid would yield the desired **4**. The results of such a successful approach are described herein.

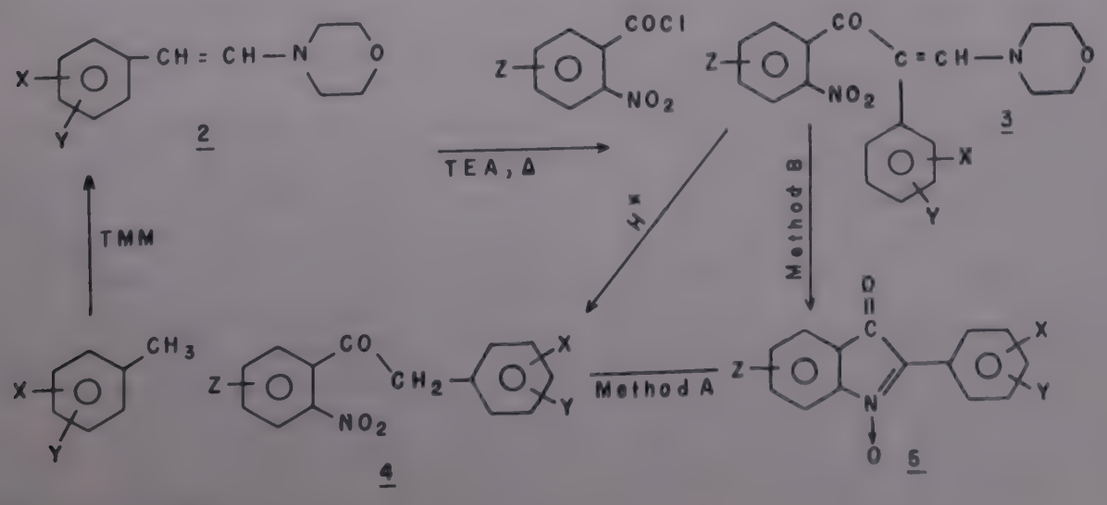
Substituted *o*- or *p*-nitrotoluenes were heated with trimorpholinomethane (TMM, 1.5 mol) under reduced pressure at 110-20° for 4 hr. The resulting *trans*-β-morpholinostyrenes (**2**) (yield 50-80%; PMR: α-H, ~δ 5.4, $J \approx 14$ Hz; IR, 1640-45 cm^{-1} for CH=CH−N≤), which were surprisingly found to be stable even in 10% aq. NaOH at room temperature for 10-12 hr, were condensed with substituted *o*-nitrobenzoyl chlorides in benzene in the presence of triethylamine under reflux for 15 hr to obtain substituted α-(*o*-nitrobenzoyl)-β-morpholinostyrenes (**3**). The structure of **3** was confirmed by the absence of α-proton in its PMR spectrum ($CDCl_3$) (IR, C=O at 1640-45 cm^{-1}) for



−C−CH=CH=N≤) and by direct hydrolysis and deformylation with 10% HCl in dioxane to **4** (PMR, $COCH_2-$, ~δ 4.2; IR, ≥C=O at 1720-25 cm^{-1}; yield 80-90%). Cyclodehydration[6] of **4** with NaOAc/EtOH/H_2O (method-A) gave 2-arylisatogens (**5**) in better than 90% yields. (IR, ≥CO at ~1710 cm^{-1}). Alternatively **3** on heating with NaOAc/AcOH/H_2O buffer (*p*H 5.5; method-B) gave **5** directly (~90% yield). However, **3** obtained from substituted *o*-nitrotoluenes did not cyclise to **5** using NaOAc/EtOH/H_2O and that others gave lower yields (~60%) compared to method-B. The intermediate compounds (**2**) and (**4**) are important as they lead to various types of heterocyclic compounds such as indoles[7], quinazolines[8], cinnolines and diazepams through *o*-nitro group[9] participation. The various isatogens synthesised are listed in Table 1.

Experimental Procedure

Melting points are uncorrected. PMR spectra were recorded on a T-60 Varian instrument with TMS as an internal standard and IR spectra on a Perkin-Elmer



†NCL Communication No. 3705.

Table 1—Characterisation Data of **2-5**

Compd	X	Y	Z	Yield %	m.p. (°C) solvent	Mol. formula (M^+)	Found (Calc) % C	H	N	^{1}H NMR (δ) $CDCl_3$/TMS int.
2a	4-NO_2	H	—	75	112 (benzene petether)	$C_{12}H_{14}N_2O_3$ (234)	61.4 (61.52)	6.10 (6.02)	12.57 (11.96)	α-H, 5.4
2b	2-NO_2	H	—	72	Liquid	$C_{12}H_{14}N_2O_3$ (234)	—	—	—	α-H, 5.4
2c	2-NO_2	5-OCH_3	—	52	Liquid	$C_{13}H_{16}N_2O_4$ (264)	—	—	—	α-H, 5.5
3a	4-NO_2	H	H	73	195 (EtOH)	$C_{19}H_{17}N_3O_6$ (383)	59.39 (59.63)	4.68 (4.47)	10.25 (10.96)	3.2(m), 3.6(m) (morpholine H)
3b	4-NO_2	H	5-OCH_3	70	183 (EtOAc + pet-Et.)	$C_{20}H_{19}N_3O_7$ (413)	57.72 (58.11)	4.75 (4.63)	10.12 (10.17)	3.1(m), 3.5(m), morpholine H 3.8 ($-OCH_3$)
3c	2-NO_2	H	H	81	208 (EtOH)	$C_{19}H_{17}N_3O_6$ (383)	59.42 (59.63)	4.69 (4.47)	10.35 (10.96)	3.3(m), 3.6(m), (morpholine H)
3d	2-NO_2	5-OCH_3	H	43	Liquid	$C_{20}H_{19}N_3O_7$ (413)	—	—	—	3.2(m), 3.6(m), (morpholine H) 3.9 (OCH_3)
3e	4-NO_2	H	4-OCH_3 5-OCH_3	33	205 (EtOH)	$C_{21}H_{21}N_3O_8$ (443)	56.48 (56.88)	4.62 (4.77)	9.52 (9.48)	3.2(m), 3.6(m), (morpholine H), 3.9 ($-OCH_3$)$_2$
4a	4-NO_2	H	H	84	135 (EtOH)	$C_{14}H_{10}N_2O_5$ (286)	58.78 (58.74)	3.88 (3.52)	9.51 (9.79)	4.2 ($-COCH_2-$)
4b	4-NO_2	H	5-OCH_3	90	155 (EtOH)	$C_{15}H_{12}N_2O_6$ (316)	56.45 (56.96)	4.08 (3.82)	9.15 (8.86)	4.2 ($COCH_2-$), 3.9 (OCH_3)
4c	2-NO_2	H	H	90	150 (EtOH)	$C_{14}H_{10}N_2O_5$ (286)	58.60 (58.74)	3.98 (3.52)	10.10 (9.79)	4.2 ($-COCH_2-$)
4d	2-NO_2	5-OCH_3	H	87	95 (EtOH)	$C_{15}H_{12}N_2O_6$ (316)	56.89 (56.96)	3.89 (3.82)	9.10 (8.86)	4.15 ($-COCH_2$), 3.9 (OCH_3)
4e	4-NO_2	H	4-OCH_3 5-OCH_3	81	195 (EtOH)[10]	$C_{16}H_{14}N_2O_7$ (346)	55.10 (55.49)	4.22 (4.08)	8.20 (8.09)	4.2 ($COCH_2$), 3.9 (OCH_3)$_2$
5a	4-NO_2	H	H	A92 B89	254[10] (Acetone)	$C_{14}H_8N_2O_4$ (268)	62.38 (62.69)	3.49 (3.01)	10.66 (10.45)	7.3-8.5 (Aromatic H)
5b	4-NO_2	H	5-OCH_3	A93 B85	205 (Acetone)	$C_{15}H_{10}N_2O_5$ (298)	60.60 (60.40)	3.74 (3.38)	9.01 (9.39)	7.2-8.5 (Aromatic H), 3.9 ($-OCH_3$)
5c	2-NO_2	H	H	A90 B90	202[11] (Acetone)	$C_{14}H_8N_2O_4$ (268)	62.67 (62.69)	3.46 (3.01)	10.70 (10.45)	7.3-8.5 (Aromatic H)
5d	2-NO_2	5-OCH_3	H	A92 B42	105 (MeOH)	$C_{15}H_{10}N_2O_5$ (298)	60.35 (60.40)	3.62 (3.38)	9.47 (9.39)	7.3-8.9 (Aromatic H), 3.9 (OCH_3)
5e	4-NO_2	H	5-OCH_3 6-OCH_3	A84 B60	255[10] (EtOH)	$C_{16}H_{12}N_2O_6$ (328)	58.30 (58.54)	3.60 (3.68)	8.66 (8.53)	7.2-8.5 (Aromatic H), 3.9 (OCH_3)$_2$

model 683 spectrophotometer, as nujol mulls, unless otherwise mentioned. Solvents and chemicals were of reagent grade. TLC plates were coatd with slurry of 200 mesh silica gel in chloroform. Solvent system for TLC was 25% ethyl acetate in benzene.

4-(Nitrophenylethenyl)morpholines or trans-β-morpholinonitrostyrenes (**2a-c**): *General procedure*

Activated nitrotoluenes (**1**, 0.01 mol) and trimorpholinomethane[12] (0.015 mol) were heated together at 120-30° under water pump suction with stirring for 4 hr until the disappearance of nitrotoluenes (as judged by TLC). The reaction products in the case of solids were crystallised from a suitable solvent. Liquids were purified by alumina chromatography.

α-(o-Nitrobenzoyl)-β-morpholinostyrenes (**3a-e**): *General procedure*

To triethylamine (0.01 mol) and **2** (0.01 mol) in dry benzene (20 ml) was added dropwise under stirring substituted *o*-nitrobenzoyl chloride (0.01 mol) in dry benzene (5 ml). The reaction mixture was refluxed under stirring for 15 hr until it showed the absence of **2** (TLC). The benzene solution was cooled, the solid separated was collected, washed with sufficient water and crystallised from a suitable solvent. When no solid separated, the benzene solution was washed thoroughly with water, dried, solvent removed and the residue purified by chromatography over alumina and the liquids obtained were used as such for the next step.

1-(*o-Nitroaryl*)-2-(*nitroaryl*)*ethanones* (**4a-e**):
General procedure

A solution of **3** (0.01 mol) in 10% aq hydrochloric acid (12.5 ml) and dioxane (50 ml) was refluxed for 2-4 hr until no starting material was shown (TLC). Dioxane was removed under reduced pressure and the solution extracted with ethyl acetate (3 × 25 ml). The combined extract was washed with water (3 × 20 ml), dried and solvent removed. The products were then crystallised from a suitable solvent.

Substituted 2-*phenylisatogens* (**5a-e**)

Method-A: *o*-Nitrophenylbenzyl ketone (**4**, 0.01 mol) was dissolved in 3:1 mixture (24 ml) of ethanol and water containing sodium acetate (0.05 mol) and refluxed over a water-bath for 4 hr. Removal of the solvent gave a solid which was collected, washed with water and crystallised from a suitable solvent.

Method-B: Compound (**3**, 0.01 mol) was refluxed with sodium acetate-acetic acid buffer (*p*H 5.5) (prepared from 2.4 g of sodium acetate, 9.2 ml water, 3.6 ml of methanol and 2.4 ml of acetic acid) for 3-4 hr. On cooling, the solid separated was collected, washed with water and crystallised from a suitable solvent.

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Synthesis of Naphtho[2,3-*h*]quinoline-7,12-dione, 1*H*-Naphtho[2,3-*h*]pyrazolo[3,4-*b*]quinoline-7,12-dione & Their Derivatives

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The Friedlander condensation of 1-amino-2-formylanthraquinone (**1**) with a number of ketones has been studied. Condensation of **1** with cyclohexanone in the presence of ethanolic KOH affords 9,10,11,12-tetrahydronaphth[2,3-*c*]acridine-5,14-dione(**2**) whereas with acetylpyridines and 2-acetylthiophene, 2-substituted naphtho[2,3-*h*]quinoline-7,12-diones (**3**) are obtained. The reaction of **1** with 3-methyl-2-pyrazolin-5-ones and oxindole under fusion gives 1*H*-naphtho[2,3-*h*]pyrazolo[3,4-*b*]quinoline-7,12-diones (**6a,b**) and 5*H*-indolo[2,3-*b*]naphtho[2,3-*h*]quinoline-5,15-(13*H*]-dione (**6c**) respectively. Reactions of **1** with other compounds have also been studied.

Besides a review[1] on the chemistry *o*-aminoaldehyde, some studies[2-5] on *o*-aminoheterocyclic aldehydes have also been reported in recent years. We report in this paper the results of our study on the Friedlander condensation of 1-amino-2-formylanthraquinone (**1**) with (a) cyclic ketones, (b) aromatic ketones such as acetophenone, acetylpyridines and 2-acetylthiophene, and (c) active methylene compounds such as oxindole, 3-methyl-2-pyrazolin-5-ones, malononitrile and ethyl cyanoacetate.

The reaction of cyclohexanone with **1** in the presence of ethanolic potassium hydroxide gave rise to 9,10,11,12-tetrahydronaphth[2,3-*c*]-acridine-5,14-dione (**2**), the structure of which was assigned on the basis of elemental analysis and spectral data (*cf.* Table 1).

Condensation of (**1**) with 2-, 3- and 4-acetylpyridines or 2-acetylthiophene under similar conditions afforded 2-substituted naphtho[2,3-*h*]quinoline-7,12-diones (**3a-d**) in 30-97% yields. The structures of these products were also elucidated on the basis of their elemental analyses and spectral data (*cf.* Table 1).

However, the aminoaldehyde (**1**) did not give a cyclic product with acetophenone and instead the condensation derivative 1-amino-2-(2-benzoylethenyl)-anthraquinoone (**4**) was formed.

The nature of the product from the reaction of (**1**) with active methylene compounds was found to depend on experimental conditions. In the presence of ethanolic potassium hydroxide the aminoaldehyde (**1**) underwent normal aldol condensation with 3-methyl-2-pyrazolin-5-one, 3-methyl-1-phenyl-2-pyrazolin-5-

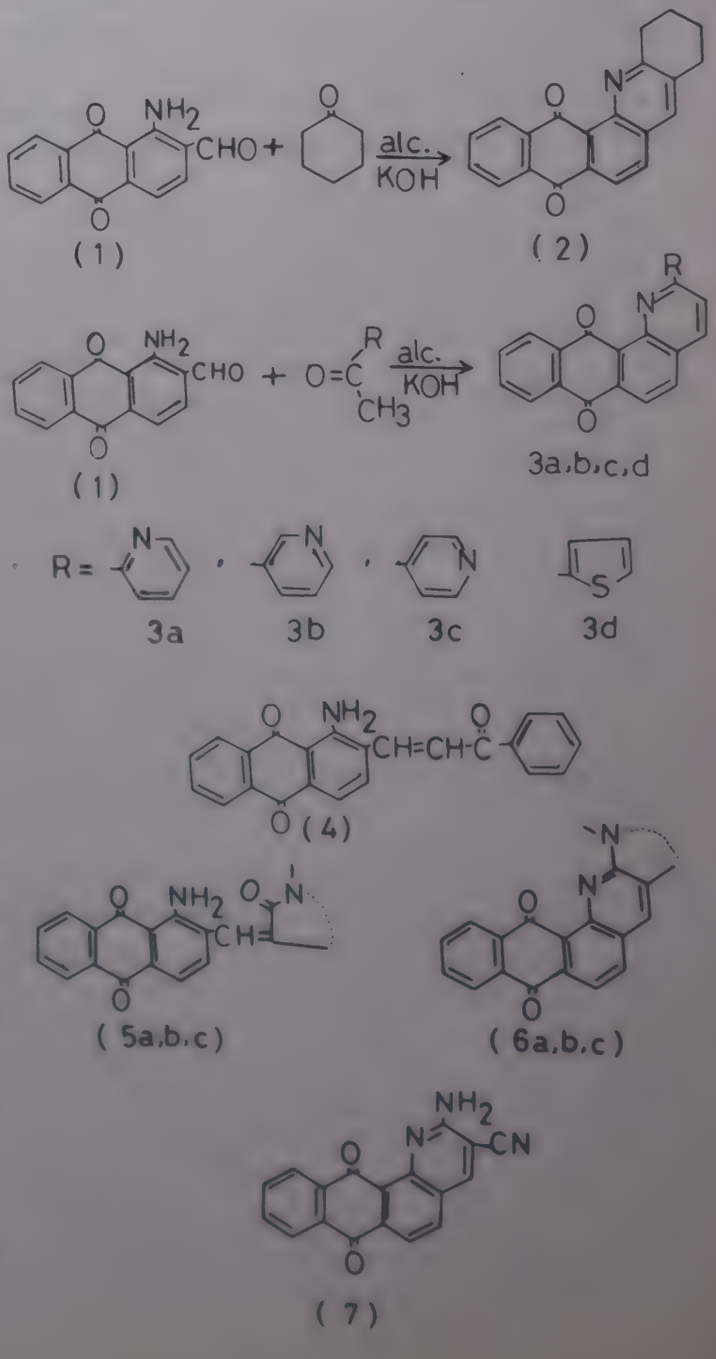

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Table 1 – Characterization Data of Various Compounds Prepared

Compd*	Yield (%)	Crystallized from	m.p. °C	Mol. formula	Found (%) (Calc.)			PMR (DMSO) (δ, ppm)	UV (DMSO) nm (log ε)
					C	H	N		
2	80	DMF	>270	$C_{21}H_{15}NO_2$	79.8 (79.0	4.3 4.8	4.2 4.5)	—	230(3.732), 450(3.544)
3a	96	Ethanol	225	$C_{22}H_{12}N_2O_2$	78.2 (78.6	3.9 3.6	8.8 8.3)	7.9-8.2 (*m*,12H,Ar-*H*)	400sh(4.591), 475(4.532), 540(4.591)
3b	30	DMF	>270	$C_{22}H_{12}N_2O_2$	78.0 (78.6	3.2 3.6	8.4 8.3)	—	410sh(3.732), 485(3.681), 540(3.663)
3c	60	DMF-H_2O	>270	$C_{22}H_{12}N_2O_2$	78.3 (78.6	3.3 3.6	8.6 8.3)	—	320sh(4.146), 440(4.114)
3d	66	DMF	210	$C_{21}H_{11}NO_2S$	73.4 (73.9	3.3 3.2	4.6 4.1)	—	312(4.255), 460(4.580)
4	64	DMF-H_2O	193-94	$C_{23}H_{15}NO_3$	78.0 (78.2	4.3 4.2	4.2 4.0)	—	213(4.431), 440(4.146)
5a	98	DMF-H_2O	185	$C_{19}H_{11}N_3O_3$	69.1 (69.3	3.5 3.3	12.7 12.8)	7.8-8.2 (*m*,6H, Ar-*H*), 2.7(*s*, 3H, CH_3), 10.8 (*s*,NH), 7.6(*s*, NH_2)	330(4.491), 450(4.455)
5b	56	Ethanol	152	$C_{25}H_{15}N_3O_3$	74.0 (74.1	3.4 3.7	10.0 10.4)	7.9-8.3 (*m*,11H, Ar-*H*), 2.7(*s*,3H, CH_3), 7.6(*s*,NH_2)	360(4.634), 470(4.462)
5c	78	ACOH-H_2O	195	$C_{23}H_{14}N_2O_3$	74.0 (74.4	4.0 3.8	7.5 7.7)	7.95-8.3(*m*,10H, Ar-*H*), 10.9(*s*, NH), 7.7(*s*,NH_2)	340(4.519), 440(3.431)
6a	95	DMF	265-66	$C_{19}H_{11}N_3O_2$	73.1 (72.8	3.4 3.5	12.9 13.4)	7.9-8.2(*m*,7H, Ar-*H*), 2.7(*s*,3H, CH_3), 10.9(*s*,NH)	230(4.455), 455(4.146)
6b	89	Anisol-pet. ether (60-80°)	205	$C_{25}H_{15}N_3O_2$	77.0 (77.1	3.7 3.9	10.3 10.8)	8-8.3(*m*,12H, Ar-*H*), 2.76(*s*, 3H,CH_3)	220(4.447), 450(4.176)
6c	86	DMF	220	$C_{23}H_{12}N_2O_2$	79.4 (79.3	3.2 3.4	8.4 8.0)	8-82(*m*,11H, Ar-*H*), 10.9 (*s*,NH)	214(4.431),
7	75	ACOH-H_2O	233-35	$C_{18}H_9N_3O_2$	71.9 (72.2	3.1 3.0	14.2 14.0)	7.9-8.3 (*m*,7H, Ar-*H*), 7.8(*s*, NH_2)	218(4.349), 427(3.699)

* IR spectra exhibited the characteristic absorption bands for $>C=O$ at ~1610; $>C=N$ at 1580; Nh at 3150; and NH_2 at 3300-3420 cm^{-1} (ref. 7).

one and oxindole followed by elimination of a water molecule to give 1-amino-2-[(3-methyl-5-oxo-2-pyrazolin-4-ylidene)methyl]anthraquinone (**5a**), 1 amino-2-[(3 -methyl-5-oxo-1-phenyl-2-pyrazolin-4 ylidene)methyl]anthraquinone (**5b**) and 1-amino-2 [(2-oxo-3-indolinylidene) methyl]anthraquinone (**5c**) respectively. However, fusion of the reactants alone for a few minutes afforded the pyridine cyclic products: 3 methyl-1*H*-naphtho [2,3-*h*] pyrazolo [3,4-*b*]quinoline-7,12-dione (**6a**), 3-methyl-1-phenyl-1*H*-naphtho [2,3-*h*] pyrazolo [3,4-*b*] quino line-7,12-dione (**6b**) and 5*H*-indolo [2,3-*b*] naptho [2,3-*h*] quinoline-5,15(13*H*)-dione (**6c**).

The structural assignments of (**6**) were based on elemental analyses and spectral data (*cf.* Table 1).

The formation of (**5**) is supported by the general findings of Majewich[6] and alain *et al.* (see ref. 4) that condensation of acetylindolin-3-one with 6-methyl-4-aminopyridazin-3-carboxaldehyde in ethanolic potassium hydroxide does not give a cyclization product.

With malononitrile in the presence of ethanolic potassium hydroxide, cyclisation occurred to give 2-amino-7,12-dihydro-7,12-dioxonaphtho[2,3-*h*] quinoline-3-carbonitrile (**7**). However no reaction took place between **1** and ethyl cyanoacetate under this condition.

Experimental Procedure

Melting points are uncorrected. PMR spectra were

recorded on a Varian XL-100 spectrometer, IR spectra on a Perkin-Elmer model 21 spectrophotometer and electronic spectra on a Varian-Cary 219 spectrophotometer.

1-Amino-2-formylanthraquinone (**1**) was prepared according to the literature procedure[8].

Reaction of **1** *with cyclohexanone, acetyl derivatives and active methylene compounds in the presence of ethanolic potassium hydroxide: General procedure*

To 1-amino-2-formylanthraquinone (**1**) (502 mg, 0.002 mol) in ethanol (20 ml) appropriate cyclic ketone, acetyl derivative or active methylene compound (0.002 mol) and 10% ethanolic solution of potassium hydroxide (0.5 mol) were added and the reaction mixture was refluxed for 2 hr, concentrated and cooled. The precipitated product was collected and crystallised from a proper solvent. The results are given in Table 1.

Reaction of **1** *with active methylene compounds under fusion: General procedure*

Equimolar amounts of **1** (0.002 mol) and the active methylene compound (0.002 mol) were ground together and heated at 150° in an oil-bath. Foaming resulted on fusion and black colour appeared. When no more gases were evolved, heating was discontinued and the resultant solid washed with pet. ether (40-60°) and crystallised from a polar solvent. The results are summarised in Table 1.

Acknowledgement

The authors are thankful to Mr Kurt L Loening, the Nomenclature Director of the Chemical Abstracts Service for naming the products which are reported in this paper.

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Synthesis of Coumarino[4′,3′:3,4]isocoumarins, Coumarino[7′,6′:3,4]isocoumarins & Dibenzo-α-pyrones

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Substituted coumarino[4′,3′:3,4]isocoumarins (IIa-d), dibenzo-α-pyrones (III, V, VIII) and coumarino[7′,6′:3,4]isocoumarins (IV, VI, VIII) have been synthesised by the condensation of reactive phenols with 2-bromobenzoic acid in the presence of copper sulphate as catalyst, and their structures established by chemical and spectral data. Useful physiological properties of these compounds have also been evaluated and discussed.

Isocoumarins and dibenzo-α-pyrones are known to exhibit estrogenic[1] and antibacterial activities and also act as phytoalexins[2]. It was therefore considered worthwhile to undertake the title study.

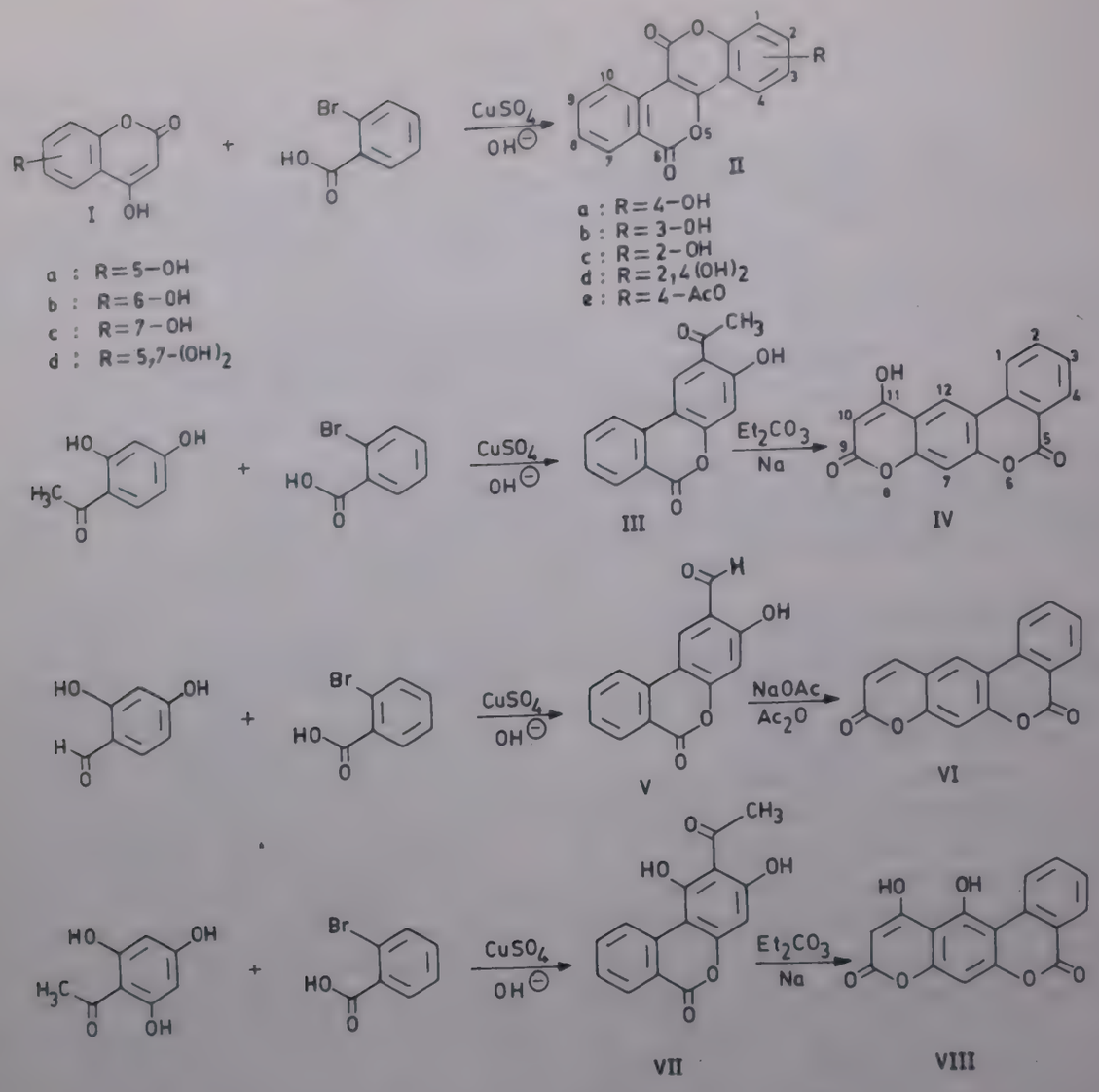
In our earlier communication[3], a new synthesis of coumarino[4′,3′:3,4]isocoumarin was reported involving condensation of sodio derivatives of 4-hydroxycoumarins with 2-bromobenzoic acid in the presence of catalytic amounts of copper sulphate. In this reaction 4-hydroxycoumarins behaved like typical reactive phenols as they underwent Pechmann[4] condensation and diazocoupling[5] reaction. This reaction has now been extended to other reactive compounds, namely oxygenated 4-hydroxycoumarins and phenols such as resacetophenone, β-resorcylaldehyde and phloracetophenone. The products formed were characterised on the basis of chemical and spectral data as coumarino[4′,3′:3,4]isocoumarins and dibenzo-α-pyrones (III, V, VII) respectively. The dibenzo-α-pyrones were subsequently converted into coumarino[7′,6′:3,4]isocoumarins (IV, VI and VIII respectively).

As a representative case, 4,5-dihydroxycoumarin was condensed with 2-bromobenzoic acid in the presence of a base under the catalytic influence of copper sulphate to give a TLC-pure colourless product (m.p. 199°). As this compound was insoluble in most of the organic solvents, its acetate was prepared and its PMR and mass spectra were studied. The acetyl derivative was assigned the structure as 4-acetoxycoumarino[4′,3′:3,4]isocoumarin (IIe) on the basis of its spectral data and those of the parent compound which in turn was assigned the structure I.

Adopting the above procedure, following compounds were prepared, namely 3-hydroxy-, 2-hydroxy- and 2,4-dihydroxycoumarino[4′,3′:3,4]isocoumarins (IIb-d) from 4,5-dihydroxy-, 4,7-dihydroxy and 4,5,7-trihydroxycoumarins (Ib-d), respectively. The yield of the product in all these cases was good (32-72%). There was no effect of hydroxyl substituent on the yield of the final product and the condensation exclusively took place involving only 4-hydroxyl as it is more reactive than other phenolic hydroxyls.

In addition to the above hydroxycoumarins, other reactive phenols such as resacetophenone, β-resorcylaldehyde and phloracetophenone also underwent condensation with 2-bromobenzoic acid in alkaline medium in the presence of copper sulphate. When resacetophenone was treated with 2-bromobenzoic acid a homogeneous colourless product (m.p. 150°) was obtained which analysed for $C_{15}H_{10}O_4$. It gave +ve tests with ferric chloride and 2,4-DNP and showed UV absorptions at 253 (log ε 4.29) and 345 nm due to benzoyl and cinnamoyl chromophores, respectively, and IR bands at 3300 (−OH), 1730 (acetyl −C=O) and 1700 cm^{-1} (coumarin −C=O). Its PMR spectrum in $CDCl_3$ exhibited signals at δ 3.0 (*s*, 3H, methyl protons), 6.4 (*s*, 1H, OH) and 7.2-7.7 (*m*, 6H, Ar−*H*). The two doublets at δ 7.2 and 7.7 (J = 1 Hz) indicated *para*-coupling. The compound on treatment with Gibbs' reagent[7,8] (2,6-dibromoquinone chlorimide) did not give a blue colour even after 1 hr indicating the absence of a free *para*-position with respect to the hydroxyl group. On the basis of the above chemical and spectral data the compound was assigned the structure 2-acetyl-3-hydroxydibenzo-α-pyrone (III). The other two possible structures were eliminated on the basis of the above chemical and spectral data, the −ve Gibbs test[7,8] and the absence of *ortho*-coupled protons in the PMR spectrum. The mass spectrum showed $M^{+\cdot}$ at m/z 254 and other ions at m/z 238, 226, 198, 182, 167, 154 and 151.

β-Resorcylaldehyde on condensation with 2-bromobenzoic acid in the presence of alkali and copper sulphate gave a colourless product (m.p. 135°) which



was found to be homogeneous (TLC single spot in benzene-ethyl acetate, 1:1) and analysed for $C_{14}H_8O_4$ (M^+ 240). It gave +ve ferric chloride and 2,4-DNP tests, and showed UV absorptions at 260 (log ε 4.32) and 338 nm (log ε 4.0) due to benzoyl and cinnamoyl chromophores, respectively, and IR bands at 3350 (−OH), 1720 (coumarin −C=O) and 1690 cm^{-1} (aldehyde −C=O). Its PMR spectrum in $CDCl_3$ displayed signals at δ 6.5 (*s*, 1H, −OH), 7.7-7.9 [*m* with close doublets (J = 1 Hz), 6H, Ar−*H*] and 10.2 (*s*, 1H, aldehyde proton). On the basis of the above chemical tests and spectral data, the structure of the compound was established as 2-formyl-3-hydroxydibenzo-α-pyrone (V). The compound (V) did not produce a blue colour with Gibbs' reagent[7,8] even after 1hr indicating the absence of a free *para*-position with respect to the hydroxyl group and thus eliminated the two alternative structures. The significant ions, besides M^+, in the mass spectrum were observed at *m/z* 212, 198, 170, 142 and 77.

Phloracetophenone and 2-bromobenzoic acid were similarly treated in alkali with catalytic amounts of copper sulphate when a colourless product (m.p. 260°) was obtained. It was found to be a single entity on TLC in ethyl acetate and analysed for $C_{15}H_{10}O_5$. The product gave +ve tests with ferric chloride and 2,4-DNP, and showed UV absorptions at 264 (log ε 4.30) and 340 nm (log ε 4.0) due to benzoyl and cinnamoyl chromophores respectively, and IR bands at 3350 (−OH), 1720 (acetyl −C=O), and 1690 cm^{-1} (lactone −C=O). Its PMR spectrum in $CDCl_3$ exhibited signals at δ 2.8 (*s*, 3H, $-COCH_3$), 6.3 (*s*, 2H, 2× −OH), and 7.2-7.6 (*m*, 5H, Ar−*H*). On the basis of the above chemical and spectral data, the compound was assigned the structure 2-acetyl-1,3-dihydroxydibenzo-α-pyrone (VII). This structure was further substantiated by immediate development of a blue colour with Gibbs' reagent[7,8] indicating the presence of a free *para*-position with respect to the hydroxyl group and thus eliminated the other possible structure. In the mass spectrum, the molecular ion was observed at *m/z* 270 besides other ions at *m/z* 254, 242, 226, 214, 198 and 158.

The unique feature in all the above dibenzo-α-pyrones is the presence of an *o*-hydroxy carbonyl system indicating that the hydroxyl group chelated with carbonyl function in the phenols is not involved in the reaction.

The dibenzo-α-pyrone III underwent condensation with diethyl carbonate in the presence of sodium under Boyd and Robertson[6] conditions to give a colourless product [m.p. 238°; TLC single spot on silica gel-G in benzene-ethyl acetate (1:1)] which showed UV absorptions at 265 nm (log ε 4.38) and 345 nm (log ε 4.31); IR bands at 3300 (−OH), 1690 and 1680 cm^{-1} (two lactone −C=O); and PMR (DMSO) signals at δ 6.6 (*s*, 1H, 10-H) and 6.7-7.1 (*m*, 6H, Ar−*H*). On the basis of these spectral data, the compound was assigned the structure 11-hydroxycoumarino[7′,6′:3,4]isocoumarin (IV).

Similarly compound V underwent cyclisation with acetic anhydride and anhyd. sodium acetate under Perkin conditions to give a colourless product (m.p. 253°; TLC single spot on silica gel-G in ethyl acetate) which showed UV absorptions at 270 (log ε 4.40) and 330 nm (log ε 4.32), and IR bands at 3300 (−OH), 1700 and 1690 cm^{-1} (two lactone −C=O). The structure of the product was established as coumarino[7′,6′:3,4]isocoumarin (VI) on the basis of the above spectral data.

2-Acetyl-1,3-dihydroxydibenzo-α-pyrone (VII) was also treated with diethyl carbonate and sodium when a colourless product was obtained (m.p. 276°; TLC single spot on silica gel-G in ethyl acetate) which showed UV absorptions at 272 (log ε 4.36) and 340 nm (log ε 4.29); IR bands at 3350 (−OH), 1710 and 1680 cm^{-1} (two lactone −C=O); and PMR(DMSO) signals at δ 6.2 (*s*, 2H, 2 × −OH), 6.43 (*s*, 1H, 10-H), 7.4-7.7 (*m*, 5H, Ar−*H*). The compound also gave positive Gibbs' test[7,8] indicating the presence of a free para-position with respect to the hydroxyl group. All these chemical and spectral data led to the structure of the product as 11,12-dihydroxycoumarino-[7′,6′:3,4]isocoumarin (VIII).

Physiological activity

All the compounds synthesized were screened for their antibacterial (tube dilution method) and antifungal (plate method) activities and were found to be active. The most active among the compounds tested for antibacterial activity against *S. aureus* and *E. coli* were 4-hydroxycoumarino[4′,3′:3,4]isocoumarin (IIa), 2,4-diacetoxycoumarino[4′,3′:3,4]isocoumarin (IId diacetate), 11-hydroxycoumarino[7′,6′:3,4]isocoumarin (IV), 11-acetoxycoumarino[7′,6′:3,4]isocoumarin (IV acetate) and 11,12-diacetoxycoumarino[7′,6′:3,4]isocoumarin (VIII diacetate) at 100 ppm concentration. The most active among the compounds tested for antifungal activity against *A. niger* were VIII diacetate, (52% inhibition), 2-acetoxycoumarino[4′,3′:3,4]isocoumarin (Ic acetate) (43.2%), IV acetate (42.6%) and 3-acetoxycoumarino[4′,3′:3,4]isocoumarin (Ib acetate) (41%) at 100 ppm concentration.

Experimental Procedure

Melting points were determined in open capillaries and are uncorrected. Unless otherwise stated, IR spectra (ν_{max} in cm^{-1}) were recorded in $CHCl_3$ on a Perkin-Elmer infracord model 337, PMR spectra on Varian A-60 D spectrometer (chemical shifts in δ-scale downfield from TMS as internal standard) and mass spectra on a Perkin-Elmer Hitachi-RMU-6L double focussing mass spectrometer at 70 eV using direct inlet system. TLC was performed on silica gel-G.

4-*Hydroxycoumarino*[4′,3′:3,4]*isocoumarin* (*IIa*)

To a mixture of 4,5-dihydroxycoumarin (Ia; 1.8 g, 0.01 mol) and 2-bromobenzoic acid (2.0 g, 0.01 mole) was added 2% aq. solution of NaOH (0.8 g in 40 ml water) to dissolve the mixture. The reaction mixture was heated on a gentle flame to reflux and a hot 2% copper sulphate solution added to it dropwise. Refluxing was continued for another 10 min and the resultant precipitate filtered while hot and washed with dil. HCl to remove copper salts. The colourless precipitate was filtered, dried and recrystallised from methanol to give IIa, m.p. 199°, yield 33%; gave single spot on TLC in ethyl acetate (Found: C, 68.6; H, 2.8. $C_{16}H_8O_5$ requires C, 68.6; H, 2.9%); UV(MeOH): 258 (log ε 4.32, benzoyl chromophore), 310 (log ε 4.18, stilbene type chromophore), 355 (log ε 4.20, α,β-unsaturated carbonyl) and 360 nm (log ε 4.29, extended conjugation); IR: 3400 (−OH), 1720 and 1690 (lactone carbonyl).

It formed an acetyl derivative (IIe) with Ac_2O/pyridine under reflux (2 hr), m.p. 182° (from EtOAc), yield 78% (Found: C, 67.0; H, 3.1. $C_{18}H_{10}O_6$ requires C, 67.1; H, 3.1%); $M^{+\cdot}$ at *m/z* 322; IR: 1750 (acetate C=O), 1725 and 1700 (lactone carbonyls); PMR($CDCl_3$): 2.5 (*s*, 3H, $-COCH_3$) and 7.4-8.3 (*m*, 7H, Ar−*H*).

3-*Hydroxycoumarino*[4′,3′:3,4]*isocoumarin* (*IIb*)

It was prepared by the above procedure from the reaction of Ib with 2-bromobenzoic acid, m.p. 226°, yield 68% (Found: C, 68.5; H, 2.9. $C_{16}H_8O_5$ requires C, 68.6; H, 2.9%); UV(MeOH): 245 nm (log ε 4.1), 310 nm (4.18), 335 nm (4.20) and 360 nm (4.29); IR: 3400 (−OH), 1720, 1690 (lactone carbonyls) formed an acetate: m.p. 210° (Found: C, 67.1; H, 3.1. $C_{18}H_{10}O_6$ requires C, 67.1; H, 3.1%).

2-*Hydroxycoumarino*[4′,3′:3,4]*isocoumarin* (*IIc*)

It was prepared by the above procedure from Ic, m.p. 243° yield 72% (Found: C, 68.5; H, 2.8. $C_{16}H_8O_5$ requires C, 68.6; H, 2.9%); UV(MeOH): 260 (log ε 4.1), 325 (3.9), 342 (4.2) and 360 nm (4.2); IR: 3380 (−OH), 1760, 1700 (lactone carbonyls); formed an acetate: m.p. 215° (Found: C, 67.1; H, 3.1. $C_{18}H_{10}O_6$ requires C, 67.1; H, 3.1%).

2,4-Dihydroxycoumarino[4',3':3,4]*isocoumarin* (*IId*)

It was prepared by the above procedure from Id, m.p. 278°, yield 67% (Found: C, 64.8; H, 2.7. $C_{16}H_8O_6$ requires C, 64.9; H, 2.7%); UV(MeOH): 261 (log ε 3.91), 312 (4.24), 343 (4.13) and 358 nm (4.24); IR: 3400 (−OH), 1710, 1690 (lactone carbonyls); formed an acetate: m.p. 257° (Found: C, 63.2; H, 3.1. $C_{20}H_{12}O_8$ requires C, 63.2; H, 3.2%).

2-Acetyl-3-hydroxydibenzo-α-pyrone (*III*)

A solution of resacetophenone (1.5 g) and 2-bromobenzoic acid (2.0 g) in aq. NaOH (2%, 8 ml) was refluxed on a gentle flame and copper sulphate solution (2%, 20 ml) added to it dropwise when a light greenish precipitate separated out as a huge froth. The refluxing was continued for 10 min, and the resultant product filtered hot, washed with dil. HCl to remove copper salts, dried and recrystallised from benzene, m.p. 147°, yield 70% (Found: C, 70.9; H, 4.0. $C_{15}H_{10}O_4$ requires C, 70.9; H, 3.9%).

2-Formyl-3-hydroxydibenzo-α-pyrone (*V*)

A solution of β-resorcylaldehyde (1.4 g) and 2-bromobenzoic acid (2.01 g) in aq. NaOH (2%, 20 ml) was refluxed and a hot copper sulphate solution (2%, 20ml) added to it dropwise. The compound precipitated was worked-up in the usual manner and recrystallised from methanol to give V, m.p. 135°, yield 77% (Found: C, 69.8; H, 3.3. $C_{14}H_8O_4$ requires C, 70; H, 3.3%).

2-Acetyl-1,3-dihydroxydibenzo-α-pyrone (*VII*)

Phloracetophenone (1.7 g, 0.1 mol) and 2-bromobenzoic acid (2.01 g, 0.01 mol) were dissolved in aq. NaOH (2%, 10 ml) and the solution was refluxed while copper sulphate solution (2%, 20 ml) added to it dropwise. The resultant compound was worked-up in the usual way and recrystallised from methanol to give VII, m.p. 260°, yield 66% (Found: C, 66.6; H, 3.6. $C_{15}H_{10}O_5$ requires C, 66.7; H, 3.7%).

11-Hydroxycoumarino[7',6':3,4]*isocoumarin* (*IV*)

A solution of III (1.27 g) in diethyl carbonate (20 ml) was added in small instalments to pulverised sodium metal (0.12 g) under anhyd. conditions. After the addition was over, the reaction mixture was heated on a water-bath for 12 hr. The unreacted sodium metal was destroyed with methanol and the solution poured into water (200 ml) and acidified with dil. HCl to precipitate IV which was filtered, washed with water, dried and recrystallised from chloroform, m.p. 238°, yield 58% (Found: C, 68.5; H, 2.8. $C_{16}H_8O_5$ requires C, 68.6; H, 2.9%); formed an acetate: m.p. 226° (Found: C, 67.1; H, 3.1. $C_{18}H_{10}O_6$ requires C, 67.1; H, 3.1%).

Coumarino[7',6':3,4]*isocoumarin* (*VI*)

A mixture of V (1.2 g), acetic anhydride (6.5 ml) and anhyd. sodium acetate (4 g) was refluxed in an oil-bath for 8 hr and poured into ice cold water. The precipitated VI was filtered, dried and recrystallised from ethanol, m.p. 253°, yield 57% (Found: C, 72.7; H, 3.1. $C_{16}H_8O_4$ requires C, 72.7; H, 3.0%).

11,12-Dihydroxycoumarino[7',6':3,4]*isocoumarin* (*VIII*)

A solution of VII (1.35 g) in diethyl carbonate (20 ml) was added slowly to pulverised sodium (0.12 g) in small instalments. The reaction mixture was refluxed for 4 hr and worked-up in the usual manner to get VIII which recrystallised from ethanol, m.p. 276°, yield 45% (Found: C, 64.8; H, 2.7. $C_{16}H_8O_6$ requires C, 64.9; H, 2.7%); formed a diacetate: m.p. 251° (Found: C, 63.1; H, 3.1. $C_{20}H_{12}O_8$ requires C, 63.2; H, 3.2%).

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Aromatic Benzhydrylation: Part IX†—Synthesis of Nuclear Benzhydrylated 4-Methylcoumarins & 4-Hydroxy-3-phenylcoumarins

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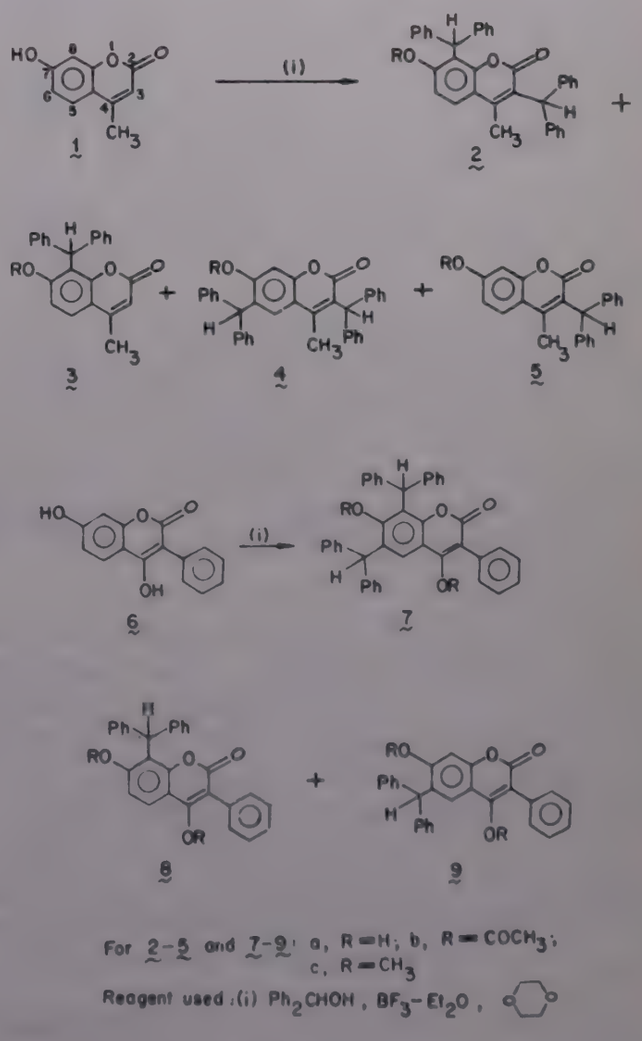
Diphenylcarbinol has been reacted with 7-hydroxy-4-methylcoumarin (**1**) and 4,7-dihydroxy-3-phenylcoumarin (**6**) separately in the presence of Lewis acid; the former affords a mixture of 3,8-bis-diphenylmethyl (**2a**, 10.5% yield), 8-diphenylmethyl (**3a**, 12.4%), 3,6-bis-diphenylmethyl (**4a**, 5.2%) and 3-diphenylmethyl derivatives (**5a**, 9.3%) showing considerable reactivity of position-3; whereas the latter gives a mixture of 6,8-bis-diphenylmethyl (**7a**, 15.4%), 8-diphenylmethyl (**8a**, 9.3%) and 6-diphenylmethyl (**9a**, 5.6%) derivatives.

As a part of our programme on the synthesis of triarylmethane types of polyphenols, 7-hydroxy-4-methyl- and 4,7-dihydroxy-3-phenyl-coumarins (**1** and **6**) were reacted with diphenylcarbinol in the presence of BF_3-Et_2O and dioxan. The coumarin **1**[2] afforded two isomeric bis-diphenylmethyl derivatives (**A** and **C**) and two isomeric mono-diphenylmethyl derivatives (**B** and **D**) as shown by the formation of their acetates and methyl ethers and also by their elemental analyses and PMR spectra. Since two aromatic protons were *ortho*-coupled ($J = 10$ Hz) in the PMR spectra of **A** and its derivatives, product **A** was assigned the structure 3,8-bis-diphenylmethyl derivative (**2a**); whereas **C** and its derivatives showed only two singlets and hence **C** was considered to be 3,6-bis-diphenylmethyl derivative (**4a**). Similarly, the PMR spectra of product **B** and its derivatives showing C_3-H as a singlet at δ 6.07 and two *ortho*-coupled aromatic protons as two doublets at 6.95 and 7.54 led to the structure of **B** as 8-*C*-diphenylmethyl derivatives(**3a**). However, the absence of C_3-H but the presence of all the three aromatic protons of the starting compound in product **D** enabled us to assign the structure of **D** as 3-diphenylmethyl derivative (**5**). It may therefore be concluded that position-3 in coumarins is as reactive as aromatic positions.

A parallel benzhydrylation of 4,7-dihydroxy-3-phenylcoumarin[3] (**6**) resulted in a mixture of only three products which were characterised as 6,8-bis-diphenylmethyl (**7a**), 8-diphenylmethyl (**8a**) and 6-diphenylmethyl (**9a**) derivatives on the basis of the formation of their diacetates, dimethyl ethers and their elemental analyses and PMR spectra.



Experimental Procedure

R_f valués refer to TLC in (A) benzene, (B) benzene-ethyl acetate (19:1), (C) benzene-ethyl acetate (9:1) or (D) benzene-ethyl acetate (17:3); UV spectra were recorded in methanol on a Perkin-Elmer model 554 spectrophotometer (λ_{max} in nm and logε in

†For Part VIII of the series, see ref. 1.

parentheses): IR spectra were recorded in KBr on a Perkin-Elmer model 599B spectrophotometer (ν_{max} in cm^{-1}); chemical shifts in PMR spectra are expressed in δ, ppm and J values in Hz.

Reaction of 7-hydroxy-4-methylcoumarin (**1**) *with diphenylcarbinol*

To a solution of **1**[2] (4.5 g, 25.5 mmol) and diphenylcarbinol (4.69 g, 25.5 mmol) in anhyd. dioxan (400 ml) was added BF_3-etherate (40 ml) with stirring. After 4 hr, the solution was diluted with ether (400 ml) and the ether layer washed with water, evaporated and the residue subjected to column chromatography. On successive elution of the column with (i) pet. ether-benzene (6:4), (ii) pet. ether-benzene (4:6), (iii) pet. ether-benzene (2:8), (iv) benzene and (v) benzene-ethyl acetate (19:1), five fractions (I-V) were obtained.

Fraction I—It crystallised from methanol to give 3,8-bis-diphenylmethyl-7-hydroxy-4-methylcoumarin (**2a**) as pale yellow crystals (1.0 g), m.p. 255-56°; R_f 0.41 (solvent-A) (Found: C, 85.2; H, 5.7. $C_{36}H_{28}O_3$ requires C, 85.0; H, 5.5%); UV: 213 (4.39) and 329 (3.94); IR: 3790, 1700, 1690 and 1620; 200 MHz PMR ($CDCl_3$): 2.24 (*s*, 3H, $-CH_3$), 5.86 (*s*, 1H, OH), 6.00, 6.40 [2*s*, 1H each, $2\times -CH(Ph)_2$], 6.78 (*d*, $J=10$, 1H, C_6-H), 7.28 (*s*, 20H, $4\times -C_6H_5$), and 7.48 (*d*, $J=10$, 1H, C_5-H).

Its acetate (**2b**), prepared by Ac_2O-Pyr method, crystallised from methanol as colourless needles, m.p. 229-30°; R_f 0.52 (solvent-A) (Found: C, 83.0; H, 5.2. $C_{38}H_{30}O_4$ requires C, 82.9; H, 5.5%); 100 MHz PMR ($CDCl_3$): 1.63 (*s*, 3H, $-OCOCH_3$), 2.24 (*s*, 3H, $-CH_3$), 6.08, 6.34 [2*s*, 1H each, $2\times -CH(Ph)_2$], 7.04 (*d*, $J=10$, 1H, C_6-H), 7.27 (*s*, 20H, $4\times -C_6H_5$) and 7.55 (*d*, $J=10$, 1H, C_5-H).

Its methyl ether (**2c**), prepared by refluxing **2a** in dry acetone with dimethyl sulphate (1 mol equiv.) and anhyd. K_2CO_3 for 1 hr, crystallised from benzene-pet. ether mixture as colourless crystals, m.p. 237-38°; R_f 0.18 (solvent-A) (Found: C, 84.8; H, 5.9. $C_{37}H_{30}O_3$ requires C, 85.0; H, 5.8%); 90 MHz PMR ($CDCl_3$): 2.21 (*s*, 3H, $-CH_3$), 3.54 (*s*, 3H, $-OCH_3$), 6.00, 6.27 [2*s*, 1H each, $2\times -CHPh_2$], 6.79 (*d*, $J=10$, 1H, C_6-H), 7.14 (*bs*, 20H, $4\times -C_6H_5$), and 7.49 (*d*, $J=10$, 1H, C_5-H).

Fraction-II—It was crystallised from benzene-ethyl acetate to give 8-diphenylmethyl-7-hydroxy-4-methylcoumarin (**3a**) as pale yellow crystals (0.8 g), m.p. 273-74°; R_f 0.18 (solvent-A) (Found: 80.4; H, 5.5. $C_{23}H_{18}O_3$ requires C, 80.7; H, 5.3%); UV: 212 (4.29) and 323 (3.80); IR: 3800, 1730, 1620 and 1445; 100 MHz PMR (DMSO-d_6): 2.33 (*s*, 3H, $-CH_3$), 6.07 (*s*, 1H, C_3-H), 6.20 [*s*, 1H, $-CH(Ph)_2$], 6.95 (*d*, $J=10$, 1H, C_6-H), 7.23 (*s*, 10H, $2\times -C_6H_5$), and 7.54 (*d*, $J=10$, 1H, C_5-H).

Its acetate (**3b**) crystallised from methanol as colourless needles, m.p. 185-86°; R_f 0.22 (solvent-A) (Found: C, 78.4; H, 5.6. $C_{25}H_{20}O_4$ requires C, 78.1; H, 5.2%); 100 MHz PMR ($CDCl_3$): 1.68 (*s*, 3H, $-OCOCH_3$), 2.40 (*s*, 3H, $-CH_3$), 6.25 (*s*, 1H, Ar $-CH\langle^{Ph}_{Ph}\rangle$), 6.32 (*s*, 1H, C_3-H), 7.0 (*d*, $J=10$, 1H, C_6-H), 7.23 (*s*, 10H, $2\times -C_6H_5$), and 7.54 (*d*, $J=10$, 1H, C_5-H).

Its methyl ether (**3c**) crystallised from benzene-pet. ether as colourless crystals, m.p. 215-16°; R_f 0.75 (solvent-A) (Found: C, 81.1; H, 5.9. $C_{24}H_{20}O_3$ requires C, 80.9; H, 5.7%); 100 MHz PMR ($CDCl_3$): 2.33 (*s*, 3H, $-CH_3$), 3.65 (*s*, 3H, $-OCH_3$), 6.20 (*s*, 1H, Ar $-CH\langle^{Ph}_{Ph}\rangle$), 6.30 (*s*, 1H, C_3-H), 6.86 (*d*, $J=10$, 1H, C_6-H), 7.23 (*s*, 10H, $2\times -C_6H_5$), and 7.50 (*d*, $J=10$, 1H, C_5-H).

Fraction-III—It crystallised from benzene-ethyl acetate to give 3,6-bis-diphenylmethyl-7-hydroxy-4-methylcoumarin (**4a**) as yellow shining plates (0.5 g), m.p. 307-08°; R_f 0.16 (solvent-B) (Found: C, 84.8; H, 5.7. $C_{36}H_{28}O_3$ requires C, 85.0; H, 5.5%); UV: 209 (4.24) and 329 (3.65); IR: 3515-3465, 1678, 1637, 1588 and 1510; 100 MHz PMR (DMSO-d_6); 2.04 (*s*, 3H, $-CH_3$), 5.82, 5.86 [2*s*, 1H each, $2\times -CH(Ph)_2$], 6.74 (*s*, 1H, C_8-H), 7.23 (*s*, 20H, $4\times -C_6H_5$) and 7.55 (*s*, 1H, C_5-H).

Its acetate (**4b**) crystallized from methanol as colourless needles, m.p. 125-26°; R_f 0.57 (solvent-B) (Found: C, 83.1; H, 5.6. $C_{38}H_{30}O_4$ requires C, 82.9; H, 5.5%); 100 MHz PMR ($CDCl_3$): 2.00 (*s*, 6H, $-CH_3$ and $-OCOCH_3$), 5.66, 6.08 [2*s*, 1H each, $2\times -CH(Ph)_2$], 7.09 (*s*, 1H, C_8-H), 7.23 (*s*, 20H, $4\times -C_6H_5$), and 7.29 (*s*, 1H, C_5-H).

Its methyl ether (**4c**) crystallised from benzene-pet. ether as colourless crystals, m.p. 140-41°; R_f 0.53 (solvent-B) (Found: C, 85.3; H, 5.8. $C_{37}H_{30}O_3$ requires C, 85.0; H, 5.8%); 90 MHz PMR ($CDCl_3$): 2.12 (*s*, 3H, $-CH_3$), 3.83 (*s*, 3H, $-OCH_3$), 5.93, 6.03 [2*s*, 1H each, $2\times -CH(Ph)_2$], 6.90 (*s*, 1H, C_8-H), 7.25 (*bs*, 20H, $4\times -C_6H_5$), and 7.55 (*s*, 1H, C_5-H).

Fraction-IV—It crystallised from benzene-ethyl acetate to give 3-diphenylmethyl-7-hydroxy-4-methylcoumarin (**5a**) as colourless crystals (0.6 g), m.p. 253-54°; R_f 0.14 (solvent-B) (Found: C, 81.1; H, 5.4. $C_{23}H_{18}O_3$ requires C, 80.7; H, 5.3%); UV: 210 (4.22) and 327 (3.91); IR: 3800, 1740, 1678, 1620, 1498 and 1460; 100 MHz PMR (DMSO-d_6): 2.30 (*s*, 3H, $-CH_3$), 5.91 ([*s*, 1H, $-CH(Ph)_2$], 6.72 (*d*, $J=2.5$, 1H, C_8-H), 6.81 (*dd*, $J=10$ and 2.5, 1H, C_6-H), 7.26 (*s*, 10H, $2\times$

$-C_6H_5$), and 7.66 (*dd*, $J=10$, 1H, C_5-H).

Its acetate (**5b**) crystallised from methanol as colourless needles, m.p. 184-85°; R_f 0.55 (solvent-B) (Found: C, 77.9; H, 5.4. $C_{25}H_{20}O_4$ requires C, 78.1; H, 5.2%); 100 MHz PMR ($CDCl_3$): 2.24 (*s*, 3H, $-OCOCH_3$), 2.32 (*s*, 3H, $-CH_3$), 6.13 [*s*, 1H, $-CH(Ph)_2$], 6.66 (*d*, $J=2.5$, 1H, C_8-H), 7.68 (*dd*, $J=10$ and 2.5, 1H, C_6-H), 7.26 (*s*, 10H, $2\times -C_6H_5$), and 7.60 (*d*, $J=10$, 1H, C_5-H).

Its methyl ether (**5c**) crystallised from benzene-pet. ether as colourless crystals, m.p. 185-86°; R_f 0.64 (solvent-B) (Found: C, 81.0; H, 5.8. $C_{24}H_{20}O_3$ requires C, 80.9; H, 5.7%); 90 MHz PMR ($CDCl_3$): 2.20 (*s*, 1H, $-CH_3$), 3.78 (*s*, 3H, $-OCH_3$), 6.07 [*s*, 1H, $-CH(Ph)_2$], 6.70 (*d*, $J=2.5$, 1H, C_8-H), 6.74 (*dd*, $J=10$ and 2.5, 1H, C_6-H), 7.20 (*s*, 10H, $2\times C_6H_5$), and 7.40 (*d*, $J=10$, 1H, C_5-H).

Fraction-V—It crystallised from 95% ethanol to afford 7-hydroxy-4-methylcoumarin (**1**) as colourless needles, m.p. 184-85° (lit.[2], m.p. 185°).

Reaction of 4,7-*dihydroxy*-3-*phenylcoumarin* (**6**) *with diphenylcarbinol*

The coumarin **6**[3] (6.45 g, 25.5 mmol), diphenylcarbinol (4.69 g, 25.5 mmol), anhyd. dioxan (400 ml) and BF_3-etherate (40 ml) were reacted and the product was worked up as in **1**. The column on elution successively with (i) pet. ether-benzene (3 : 1), (ii) pet. ether-benzene (1 : 1), (iii) pet. ether-benzene (1 : 3), (iv) benzene-ethyl acetate (19 : 1) gave four fractions (VI-IX).

Fraction-VI—It crystallised from methanol to give 6,8-bis-diphenylmethyl-4,7-dihydroxy-3-phenylcoumarin (**7a**) as a white solid (1 g), m.p. 265-66°; R_f 0.57 (solvent-C) (Found: C, 84.0; H, 5.1. $C_{41}H_{30}O_4$ requires C, 83.9; H, 5.2%); UV: 228 (4.1) and 299 (3.2); IR: 3300, 1710, 1590, 1450 and 1370; 90 MHz PMR: 5.69, 6.66 [2*s*, 1H each, $2\times -CH(Ph)_2$], and 7.00-7.34 (*bm*, 26H, $5\times -C_6H_5$ and C_5-H).

Its acetate (**7b**), prepared by Ac_2O-Pyr. method at room temperature, crystallized from methanol as a white crystalline solid, m.p. 230-32°; R_f 0.34 (solvent-A) (Found: C, 80.3; H, 5.2. $C_{45}H_{34}O_6$ requires C, 80.6; H, 5.1%); UV: 278 (3.9); IR: 2990, 1770, 1720, 1460 and 1380; 90 MHz PMR: 1.47, 1.66 (2*s*, 3H each, $2\times -OCOCH_3$), 5.41, 6.30 (2*s*, 1H each, $2\times -CH(Ph)_2$], and 7.26-7.38 (*bm*, 26H, $5\times -C_6H_5$ and C_5-H).

Its dimethyl ether (**7c**) crystallised from benzene-pet. ether mixture as colourless crystals, m.p. 218-20°; R_f 0.48 (solvent-B) (Found: C, 84.5; H, 5.0. $C_{43}H_{34}O_4$ requires C, 84.0; H, 5.5%); UV: 208 (5.00), and 319 (3.6); IR: 3390, 1720, 1600 and 1460; 90 MHz PMR (CCl_4): 3.1-3.34 (*s*, 3H each, $2\times -OCH_3$), 5.96, 6.20 (2*s*, 1H each, $2\times -CH(Ph)_2$], and 7.16-7.32 (*bm*, 26H, $5\times -C_6H_5$ and C_5-H).

Fraction-VII—It crystallised from benzene to give 8-diphenylmethyl-4,7-dihydroxy-3-phenylcoumarin (**8a**) as a colourless crystalline solid 0.8 g, m.p. 295-96°; R_f 0.56 (solvent-D) (Found: C, 79.7; H, 4.9. $C_{28}H_{20}O_4$ requires C, 80.0; H, 4.8%); UV: 227 (4.0) and 298 (4.1); IR: 3320, 1700, 1670, 1570 and 1460; 90 MHz (PMR ($CDCl_3$ + TFA): 6.45 [*s*, 1H, $-CH(Ph)_2$], 7.02 (*d*, $J=9.5$, 1H, C_5-H), 7.17-7.48 (*bm*, 15H, $3\times -C_6H_5$), and 8.01 (*d*, $J=9.5$, 1H, C_6-H).

Its acetate (**8b**) crystallised from methanol as a white crystalline solid, m.p. 205-6°; R_f 0.53 (solvent-B) (Found: C, 74.9; H, 5.0. $C_{32}H_{24}O_6$ requires C, 76.2; H, 4.8%); UV: 224 (4.2) and 270 (3.9); IR: 1780, 1720, 1590, 1450, 1370 and 1120; 90 MHz PMR: 1.66, 2.05 (2*s*, 3H each $2\times -OCOCH_3$), 6.37 [*s*, 1H, $-CH(Ph)_2$], 7.10 (*d*, $J=9.5$, 1H, C_5-H), 7.26-7.38 (*bm*, 15H, $3\times -C_6H_5$), and 7.50 (*d*, $J=9.5$, 1H, C_6-H).

Its methyl ether (**8c**), crystallised from petrol-benzene mixture as colourless crystals, m.p. 215-16°; R_f 0.69 (solvent-B) (Found: C, 80.7; H, 5.8. $C_{30}H_{24}O_4$ requires C, 80.4; H, 5.4%); UV: 209 (4.7), and 313 (3.9); IR: 2990, 1700, 1600, 1480 and 1380; 90 MHz PMR (CCl_4+CDCl_3): 3.49, 3.63 (*s*, 3H each, $2\times -OCH_3$), 6.32 [*s*, 1H, $-CH(Ph)_2$], 6.78 (*d*, $J=9.5$, 1H, C_5-H). 7.2-7.35 (*bm*. 15H. $3\times -C_6H_5$), and 7.65 (*s*, $J=9.5$, 1H, C_6-H).

Fraction-VIII—It crystallised from ethyl acetate to give 6-diphenylmethyl-4,7-dihydroxy-3-phenylcoumarin (**9a**) as a crystalline solid, m.p. 223-24°; R_f 0.35 (solvent-D) (Found: C, 80.4; H, 4.7. $C_{28}H_{20}O_4$ requires C, 80.0; H, 4.8%); UV: 214 (4.2) and 319 (3.6); IR: 3360, 1730, 1600, 1505 and 1270; PMR 5.96 [*s*, 1H, $-CH(Ph)_2$], 7.10 (*s*, 1H, C_8-H), 7.2 (*s*, 15H, $3\times -C_6H_5$), and 7.36 (*s*, 1H, C_5-H).

The acetate (**9b**), crystallised from methanol as a crystalline solid, m.p. 223-24°; R_f 0.5 (solvent-B) (Found: C, 77.2; H, 5.0. $C_{32}H_{24}O_6$ requires C, 76.2; H, 4.8%); UV: 225 (4.52), 2.43 (4.32), 254 (4.3) and 260 (4.3); IR: 2990, 1760, 1740, 1480 and 1370; PMR: 1.83, 1.9 (*s*, 3H each, $2\times -OCOCH_3$), 5.67 [*s*, 1H, $-CH(Ph)_2$], 6.80 (*s*, 1H, C_8-H), and 7.00-7.55 (*bm*, 16H, $3\times -C_6H_5$ and C_5-H).

Fraction-IX—It crystallised from 95% ethanol to afford 4,7-dihydroxy-3-phenylcoumarin (**6**) as colourless needles, m.p. and m.m.p. 283-84°.

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A Simple Economical Procedure for Selective Reduction of Aldehydes in Presence of Ketones

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A simple, efficient, and economical method for chemoselective reduction of aldehydes in the presence of ketones using stoichiometric amounts of sodium borohydride under phase-transfer catalysis is described. Aliphatic, aromatic and unsaturated aldehydes are reduced rapidly in high yields while dialkyl, aralkyl, diaryl, and cycloaliphatic ketones are practically inert under the same conditions. Some exceptions are noted. The scope of the present method is illustrated with suitable examples of selective and competitive reductions. The high reactivity of the phase-transferred borohydride species as compared to that of pre-formed quaternary ammonium borohydrides is noted.

Chemoselective[1] reduction of a formyl group in the presence of a ketonic carbonyl group is an important aspect of current synthetic methodologies. A variety of reducing agents are available for this purpose[2-18]. The practical significance of many of these methods seems, however, to be rather limited in terms of cost, time, and yield and operational simplicity. We now report a simple, rapid, and economical alternative to these methods involving the use of stoichiometric amounts of $NaBH_4$ under phase-transfer catalysis (PTC).

The chemoselective potential of $NaBH_4$ under PTC for aldehyde reductions seems to have been ignored till now inspite of the fact that ketones are relatively unreactive under these conditions[19]. The PTC method using N-dodecyl-N-methylephedrinium bromide[20] is not selective while this salt seems to function by activating C=O groups through H-bonding rather than as a phase-transfer agent. Some R_4NBH_4 have been reported[7] to selctively reduce aldehydes though Bu_4NBH_4 in CH_2Cl_2 (ref. 21) does not seem to be capable of selectivity. The uncatalysed two-phase reduction procedure[22] using $NaBH_4$ is not highly selective and it also requires relatively long reaction times for completion.

Addition of 0.26 equiv of $NaBH_4$ in minimum amount of water to a stirred solution of an aliphatic, aromatic, or unsaturated aldehyde (Chart 1) in benzene containing a concentrated aq. solution of 2.6 mol % of Bu_4NBr at 20° led to clean and rapid reduction in 30 min. Work-up after a further 30 min gave high yields of alcohols (Table 1). Toluene and CH_2Cl_2 could also be used as solvents while $PhCH_2NEt_3Cl$ and Aliquat-336 worked equally well as catalysts. Only *p*-anisaldehyde took a longer time and required a further addition of $NaBH_4$ for completion. There was negligible reduction in the absence of either water or the catalyst. Increasing the catalyst concentration to 26 mol % did not have any effect while decreasing it to 1.3 mol % led only to partial reductions. However, *p*-chlorobenzaldehyde (**1f**) could be reduced in high yield using only 1.3 mol % of Bu_4NBr with a little excess (0.026 equiv) of $NaBH_4$ added after the first 30 min. Use of Bu_4NBH_4 (0.26 equiv) in place of $NaBH_4/Bu_4NBr$ led to incomplete reductions either with benzene or CH_2Cl_2 as solvents.

$$RCHO \longrightarrow RCH_2OH$$
1 **2**

R	
a, $CH_3(CH_2)_3CHCH_2CH_3$	i, $2-NO_2C_6H_4$
b, $CH_3(CH_2)_6$	j, $PhCH=CH$
c, Ph	k, $4-Cl-2-NO_2C_6H_3$
d, $3-CH_3OC_6H_4$	l, $4-BrC_6H_4$
e, $4-CH_3OC_6H_4$	m, $3,4-(OCH_3)_2C_6H_3$
f, $4-ClC_6H_4$	n, $4-PhCOC_6H_4$
g, $4-CH_3C_6H_4$	o, PhCO
h, $4-NO_2C_6H_4$	

CHART 1

In contrast to the facile reduction of aldehydes many aliphatic and aromatic methyl ketones, benzophenones and a 1, 3-diketone (Chart 2) were either inert or only negligibly affected under the same conditions (Table 2). It took 48 hr to get an 80% yield of the alcohol from acetophenone. Cyclohexanone (**3l**) and 4-nitrobenzophenone (**3h**) were, however, exceptionally reactive, the latter being nearly

Table 1—Reduction of Aldehydes (1) Using $NaBH_4$ under PTC Conditions[a]

Compd (0.02 mol)	Time (hr)	Catalyst (mol %)	Temp. (°C)	Yield[b] (%)
2a	1	2.6	20-25	85
2b	1	2.6	20-25	90
2c	1	2.6	20-25	75
2d	1	2.6	20-25	90
2e[c]	3	2.6	20-25	85
2f	1	2.6	20-25	90
2f	1.25	1.3	20-25	90[d]
2g	1	2.6	20-25	90
2h	1	2.6	20-25	75[e]
2i	1	2.6	20-25	87
2j[f]	1.75	2.6	20-25	86
2k	1	2.6	20-25	85
2l	1	2.6	20-25	88
2m	1	2.6	20-25	90
2n[g]	1	2.6	20-25	87
2o[g]	1	2.6	20-25	63

(a) Molar ratio of aldehyde, $NaBH_4$ and $Bu_4NBr = 1:0.26:0.026$. Solvent was benzene. (toluene or CH_2Cl_2 could also be used as solvents).

(b) Yield after distillation *in vacuo* in kugel-rohr apparatus.

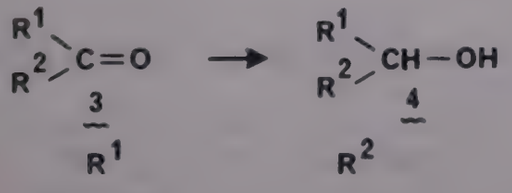
(c) An additional 0.052 equiv of $NaBH_4$ and a corresponding excess of Bu_4NBr were used.

(d) Additional 0.026 equiv of $NaBH_4$ was added after 30 min.

(e) Yield after crystallisation, m.p. 92-94°.

(f) 10% excess of $NaBH_4$ was used.

(g) No aldehyde peak in PMR spectrum.



	R^1	R^2
a,	$PhCH_2CH_2$	CH_3
b,	$(CH_3)_2CHCH_2$	CH_3
c,	Ph	CH_3
d,	$4-CH_3C_6H_4$	CH_3
e,	Ph	Ph
f,	$4-ClC_6H_4$	Ph
g,	$4-CH_3C_6H_4$	Ph
h,	$4-NO_2C_6H_4$	Ph
i,	$PhCOCH_2$	Ph
j,	$PhCH=CH$	Ph
k,	$PhCH=CH$	CH_3
l,	$-(CH_2)_5-$	
m,	$4-ClC_6H_4$	CH_2CH_2COOH

CHART 2

Table 2—Reduction of Ketones (3) Using $NaBH_4$ under PTC Conditions[a]

Compd (0.02 mol)	Time (hr)	Catalyst (mol %)	Temp. (°C)	Recovered ketone (%)[b]	Yield of 4 (%)
3a	1	2.6	20-25	95	—
3b	1	2.6	20-25	95	—
3c	1	2.6	20-25	85	15
3c	1	1.3	20-25	96[h]	—
3c	48	2.6	20-25	—	80
3c	1	2.6	20-25	—	95[b,c]
3d	1	2.6	20-25	95	—
3e	1	2.6	20-25	96	—
3f	1	2.6	20-25	96	—
3g	1	2.6	20-25	95	—
3h	1	2.6	20-25	—	90[d]
3i	1	2.6	20-25	90	—
3j	1	2.6	20-25	—[e]	—
3k	1	2.6	20-25	51[f]	—
3l	1	2.6	20-25	—	75-77[g]
3l	1	1.3	20-25	92[h]	—
3m[i]	1	2.6	20-25	—	73[j]

(a) Molar ratio of ketone, $NaBH_4$ and Bu_4NBr same as in Table 1; solvent was benzene.

(b) By PMR analysis of crude reaction mixtures using pure ketones as standards.

(c) Complete reductions observed using water as medium, or by using 1 molar equiv of $NaBH_4$ and Bu_4NBr in water-benzene.

(d) m.p. 72-73° (rep.[25] m.p. 74°).

(e) Mixture of products.

(f) Estimated by UV spectroscopy; λ_{max}^{MeOH} 285 nm (ε 28,905) for the pure ketone.

(g) Cyclohexanone was isolated as the bisulphite adduct. Cyclohexanol was isolated by extraction with organic solvent.

(h) TLC & IR indicate the absence of any alcohol. For details, see Experimental.

(i) Used as an aq. soln of its sodium salt.

(j) Isolated the derived γ-lactone after acid treatment and purification by silica gel chromatography.

quantitatively reduced. The amount of water in the reaction mixture was found to exert a remarkable control on the extent of ketone reductions. Thus acetophenone, cyclohexanone and the Na-salt of 3 m could in fact be reduced completely in 1 hr using water as solvent. A similar effect was noticed earlier in reductions using long-chain quaternary ammonium borohydrides[7a]. Based on these findings and using only 1.3 mol % of Bu_4NBr and decreased amounts of water acetophenone and the reactive cyclohexanone were found totally unreactive being recovered in >90% yield (see Experimental). Other cyclic aliphatic ketones can thus be expected to be similarly unreactive under these conditions. The aldehyde **1f** could, however, be reduced completely. It may be noted that there are only a few reagents[23] with the chemoselective potential of reducing aldehydes in the presence of cyclohexanone. Partial saturation of the double bond

Table 3—Competitive Reductions between Aldehydes and Ketones Using $NaBH_4$ under PTC Conditions[a]

Aldehyde or ketone (0.02 mol)	Ketone (0.02 mol)	Time (hr)	Temp. (°C)	Reduction of aldehyde (%)[b]	Recovered ketone (%)[b]
1d	**3c**	1	20-25	95	93
1d	**3d**	1	20-25	98	98
1f	**3j**	1	20-25	75[c]	94[c]
1f[d]	**3c**	1.5	0	95	90
1f[e]	**3l**	1	20-25	96	—[f]
1f	**3k**	1	20-25	94	96
3l	**3c**	1	20-25	—	96[g]

(a) Molar ratio of aldehyde or ketone, $NaBH_4$ and Bu_4NBr = 1:0.26:0.026. Solvent was benzene.

(b) Estimations by PMR spectroscopy using pure aldehydes and ketones as standards.

(c) After isolation by column chromatography on silica gel.

(d) In ether as solvent.

(e) Only 0.013 equiv of Bu_4NBr was used with an additional 0.026 equiv of $NaBH_4$ being added after 30 min.

(f) Not estimated.

(g) Acetophenone was recovered.

as well as the C=O group were observed with the conjugated ketones **3j** and **3k**.

The chemoselectivity of the present method was further demonstrated by reduction of the keto-aldehydes (**1n** and **1o**) to the ketoalcohols (**2n** and **2o**) in high yields and by competitive reductions of the aldehydes **1d** and **1f** in the presence of the ketones **3c**, **3d**, **3j**, **3k** and **3l** (Table 3). All the ketones were nearly quantitatively recovered. Interestingly, cyclohexanone could be reduced in the presence of acetophenone. In this connection it may be noted that Bu_4NBH_4 in CH_2Cl_2 (ref. 21) does not distinguish between these two ketones while they could be distinguished easily in the uncatalysed two-phase reduction procedure[22]. The high yield reduction of cinnamaldehyde (**1j**) to cinnamyl alcohol (**2j**) indicates the applicability of the present PTC method to the reduction of unsaturated aldehydes. Reduction of unsaturated aldehydes by $NaBH_4$ is known[24] to give rise to substantial amounts of saturated alcohols.

A noteworthy feature of the present method is the remarkably higher reactivity of the phase-transferred species, generated from as little as 2.6 mol % of the catalyst, than that of any of the pre-formed R_4NBH_4 towards aldehydes. Such a high reactivity is possibly associated with very minute concentrations of R_4NBH_4 generated during the reaction. A highly aqueous medium seems to enhance this activity as noted before. The fact that this PTC method works equally efficiently with benzene or CH_2Cl_2 as solvent shows that the different solubility behaviour of Bu_4NBH_4 in these solvents does not play any significant role in the reaction.

Experimental Procedure

IR spectra were recorded on a Perkin-Elmer model 597 infrared spectrophotometer and UV spectra on a Hitachi model 200 UV/vis spectrophotometer. The aldehydes and ketones used were pure materials, purified by distillation and/or chromatography. Many of the aldehydes and ketones used were prepared from the corresponding alcohols by a versatile method developed by us involving chromium trioxide and tetrabutylammonium hydrogensulphate under liquid-liquid PTC conditions[26]. Sodium borohydride used was of 98% purity.

General procedure for $NaBH_4$ reductions under PTC

To a cooled (20°) and stirred 10% solution of the aldehyde or ketone (20 mmol) in benzene containing a solution of Bu_4NBr (0.52 mmol) in water (0.32 ml) was added dropwise a solution of $NaBH_4$ (5.2 mmol) in water (0.4 ml) during 5-10 min. After addition, the reaction mixture was stirred at 20° for 1 hr and then quenched with 2 *N* HCl (3 ml). The organic layer was separated, washed (water and brine) and dried (drierite) and the solvent removed in a rotary evaporator. The crude product was generally purified by kugel-rohr distillation.

Alternatively, solid $NaBH_4$ can be added in portions to a solution of the compound and catalyst in benzene containing water (0.72 ml).

Reduction of cyclohexanone (3l) *using* 1.3 *mol % of catalyst*

To a stirred solution of **3l** (8.6 g, 0.1 mol) in benzene (125 ml) containing Bu_4NBr (0.4 g, 0.00124 mol) and water (1.5 ml) at 20° was added solid $NaBH_4$ (0.99 g, 0.026 mol) in portions during 10 min. About 30 min after addition, a further amount of $NaBH_4$ (0.099 g) was added and the reaction mixture stirred for another 30 min at 20°. Quenching and work-up gave 7.91 g unreacted cyclohexanone, free of cyclohexanol (TLC and IR spectrm). A similar result was obtained with acetophenone.

p-Chlorobenzaldehyde (**1f**) on similar reduction gave a near quantitative yield of the alcohol (**2f**). PMR ($CDCl_3$) of the γ-lactone derived from **4m**: δ 1.65-3.3 (*m*, 4H, Ar−CHCH_2 & COCH_2), 5.45 (*t*, 1H, OC*H*) and 7.25 (*s*, 4H, Ar − H); **2j**: δ 3.35 (*bs*, 1H, OH), 4.2 (*d*, 2H, *J* = 4Hz, CH_2), 6.35 (*m*, 2H, C*H*=C*H*), 7.3 (*s*, 5H, Ar − H); **4h**: δ 3.7 (*s*, 1H, OH), 5.74 (*s*, 1H, CH), 7.35, 8.05 (each *m*, 9H, Ar − H); **2n**: δ 4.7 (*s*, 2H, CH_2), 7.5 (*m*, 9H, Ar − H).

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Synthesis, Positive & Negative Ion Mass Spectra & Microbial Activity of N-Benzyltetrahydroisoquinolines†

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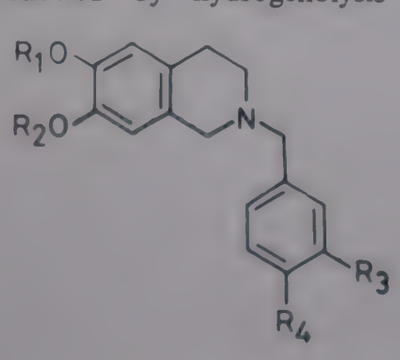
Substituted N-benzyltetrahydroisoquinolines (**5-11**) have been synthesised and their positive and negative ion mass spectra studied. The $M^{+\cdot}$ of these compounds are fairly stable and abundant RDA fragment ions (often corresponding to the base peaks) are observed in their positive ion EI spectra. However, under negative ion conditions these molecules fragment in a similar way as that of 1-benzyltetrahydroisoquinolines. The base (**5-11**) hydrochlorides when tested against a number of fungi and bacteria do not exhibit any promising activity.

Naturally occurring N-benzyltetrahydroisoquinolines are of considerable biosynthetic interest[1]. The biological activities of these bases have not been evaluated. Further, the mass fragmentation pattern of such compounds has not been studied so far. In view of these facts we report here the synthesis, positive and negative ion mass spectral studies and antibacterial and antifungal activities of some substituted N-benzyltetrahydroisoquinolines (**5-11**).

Condensation of suitably substituted phenethylamines (**1**) with substituted benzaldehydes (**2**) yielded the schiff bases (**3**) which were reduced to **4** by sodium borohydride in methanol. Reaction of **4** with formaldehyde followed by hydrogenolysis with hydrochloric acid finally afforded the desired N-benzyltetrahydroisoquinolines (**5-11**) in fairly good yields (Scheme 1).



5. $R_1, R_2 = -CH_2-$, $R_3 = R_4 = H$
6. $R_1 = R_2 = Me$, $R_3 = R_4 = H$
7. $R_1 = R_4 = Me$, $R_2 = R_3 = H$
8. $R_1 = R_2 = R_4 = Me$, $R_3 = OH$
9. $R_1 = R_4 = Me$, $R_2 = H$, $R_3 = OMe$
10. $R_1 = Me$, $R_2 = R_3 = R_4 = H$
11. $R_1 = R_4 = Me$, $R_2 = H$, $R_3 = OH$

The IR, UV, PMR and C, H and N elemental analysis of the compounds were in complete agreement with the assigned structures. None of the compound showed any promising antibacterial and antifungal activities when tested against a large number of bacteria and fungi.

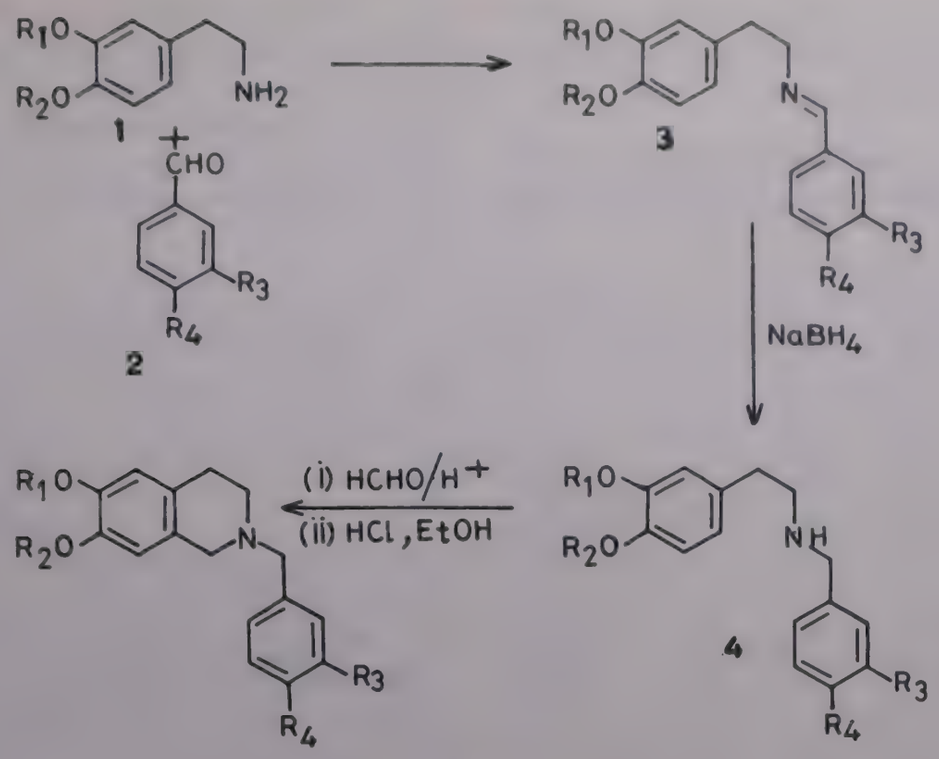
Positive and Negative Ion Mass Spectra of **5-11**

The positive ion EI spectra of 1-benzyltetrahydroisoquinolines are characterised by the absence of molecular ions[1]. The base peaks invariably correspond to the loss of the substituent on C_1, a process made facile by the doubly benzylic nature of $C_1 - C_9$ bond. However, in the N-benzyltetrahydroisoquinolines (**5-11**) this cleavage leads to the most abundant ion only in **8** and **11**, while in others it results in less prominent ions (Table 1). Unlike 1-benzyltetrahydroisoquinolines the molecular weights of N-benzyltetrahydroisoquinolines can easily be determined from their EI mass spectra as prominent $M^{+\cdot}$ peaks are observed. RDA cleavage which is practically absent in 1-

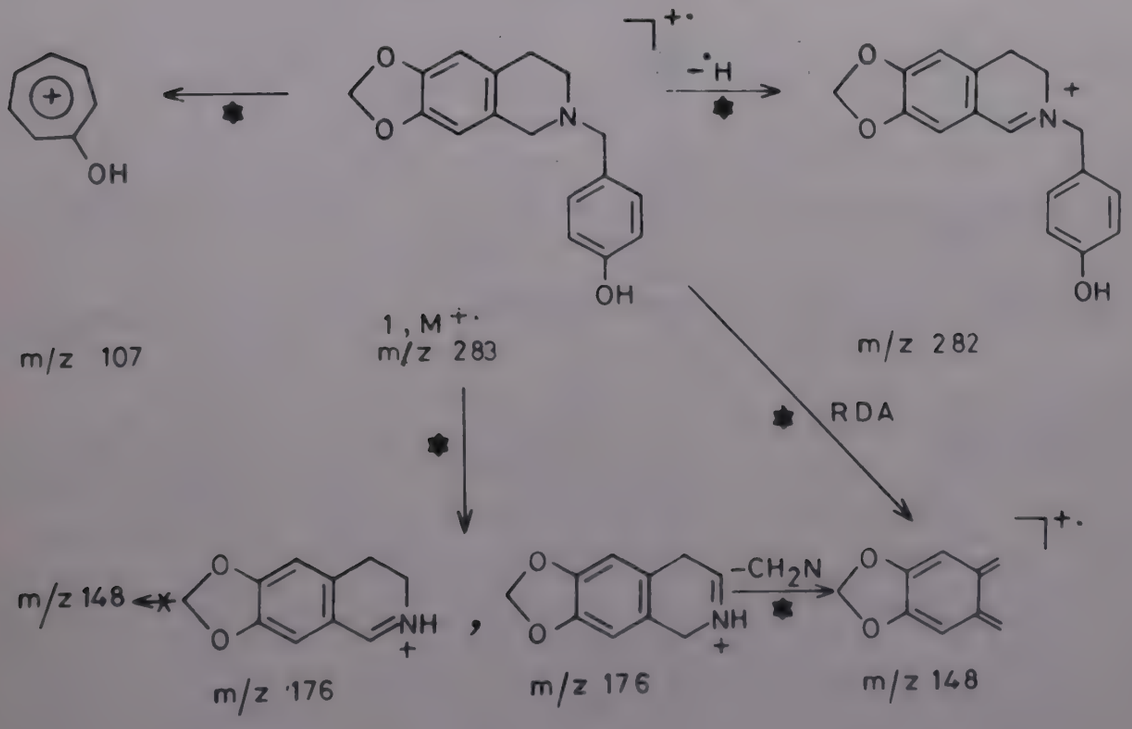
Table 1—Ion Abundances (%, in parentheses) in the Positive Ion EI Spectra of Compounds **5-11** (values in *m/z* unit)

Ion	5	6	7	8	9	10	11
M^+	283	299	299	329	329	285	315
	(32)	(22)	(20)	(10)	(4)	(38)	(10)
$(M-H)^+$	282	298	298	328	328	284	314
	(32)	(23)	(18)	(11)	(6)	(35)	(15)
Benzylic	176	192	178	192	178	178	178
cleavage	(54)	(67)	(18)	(100)	(77)	(75)	(100)
RDA	148	164	150	164	150	150	150
	(100)	(100)	(50)	(55)	(38)	(100)	(55)
Tropylium	107	107	121	137	151	107	137
	(55)	(35)	(100)	(50)	(100)	(80)	(97)

†CDRI Communication No. 3725.



Scheme 1.



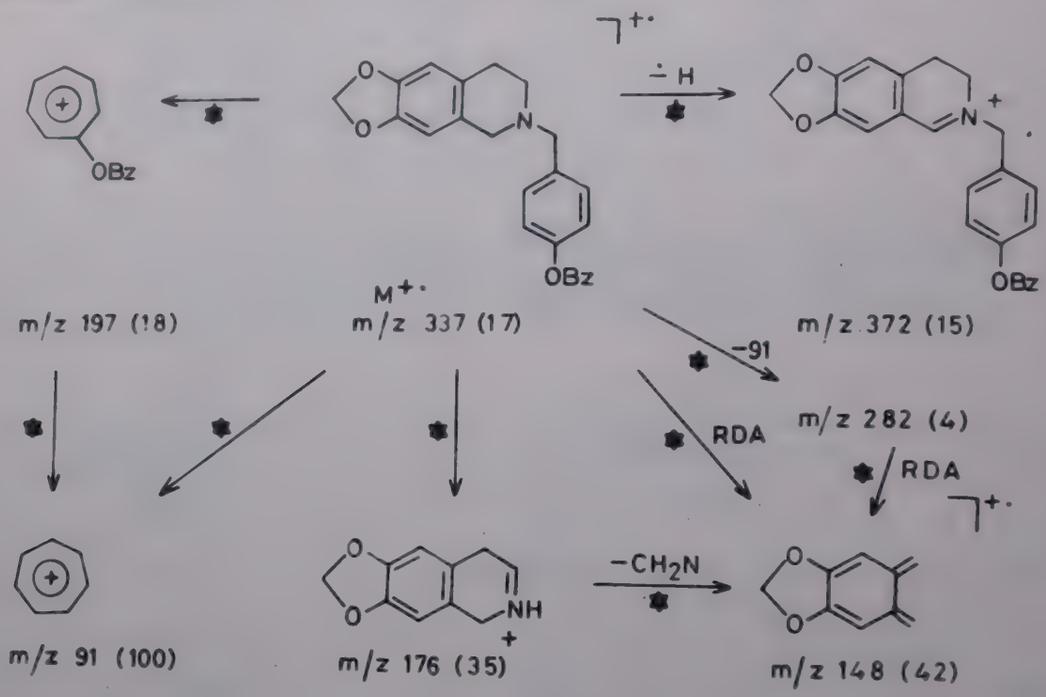
Scheme 2

benzyltetrahydroisoquinolines is one of the major pathways of fragmentation in these compounds as observed earlier in N-alkyltetrahydroisoquinolines[4,5]. The tropylium ion resulting from benzylic cleavage also gives rise to very intense peaks in the spectra. Metastable measurement by high voltage scan in **5** confirm the direct formation of the ions at *m/z* 282, 176, 148 and 107 from $M^{+\cdot}$ (Scheme 2). The elemental composition of these ions have been confirmed by exact mass measurements. The observation of metastable transition in the first field-free region by high voltage scan also confirms the formation of the RDA fragment ion at *m/z* 148 by decomposition of the ion at *m/z* 176. In earlier studies[4-6] on the EI spectra of N-substituted tetrahydroisoquinolines metastable peaks were not observed for the RDA reaction. The fact that RDA ions are not formed from the *m/z* 176 ion in the corresponding 1-benzyltetrahydroiso-

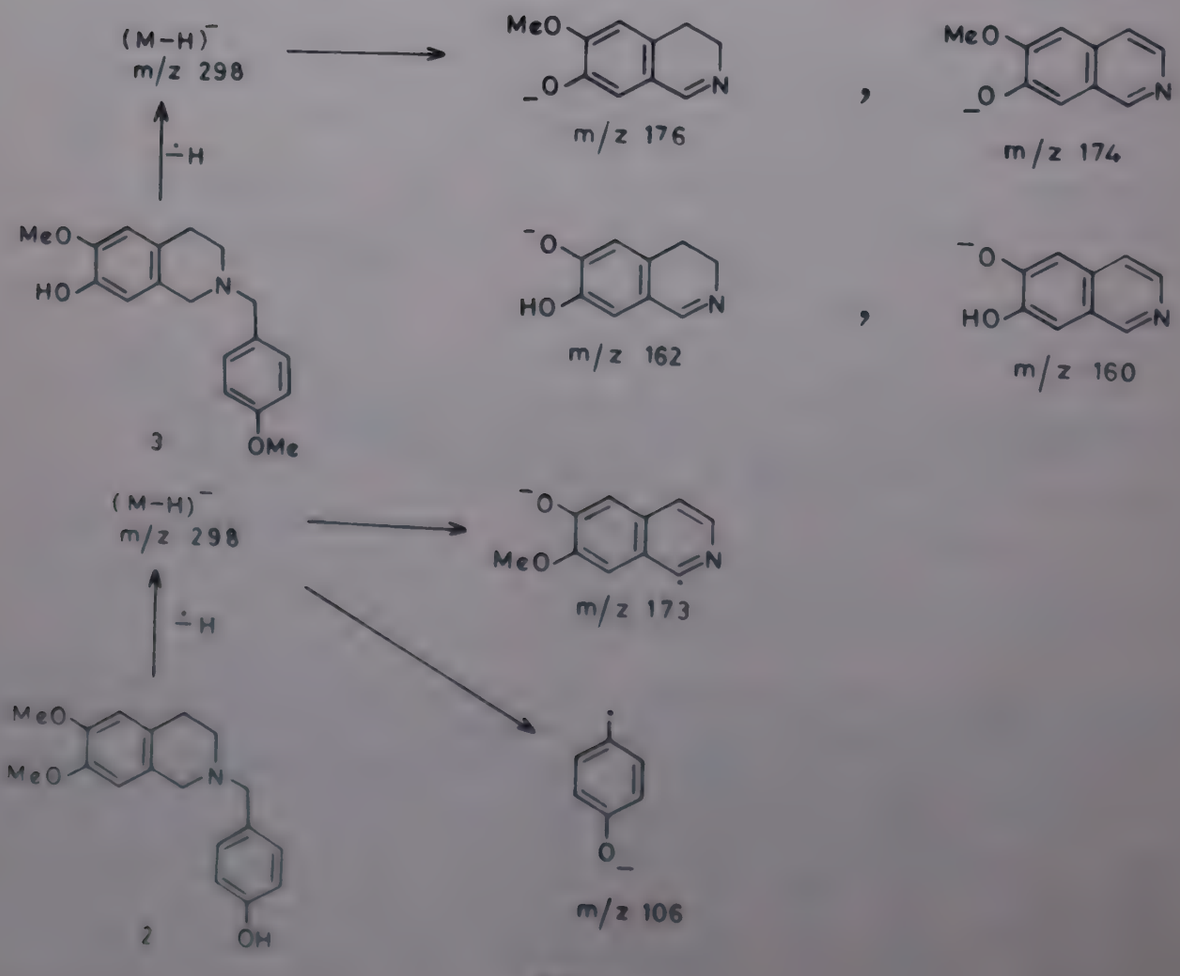
quinolines indicates different structures for the *m/z* 176 ion (Scheme 2) in 1-benzyl and N-benzyltetrahydroisoquinolines as suggested earlier in the case of sendaverin[6].

The benzylated derivatives of **5-11** behave similarly under electron impact (Scheme 3). Metastable peaks were observed for the formation of the *m/z* 148 ion (RDA fragment) from $M^{+\cdot}$, $(M-Bz)^+$ and *m/z* 176 ion in the spectrum of the benzylated derivative of **5**.

The abundances of the principal ions in the negative ion spectra of **5-11** are given in Table 2. Unlike 1-benzyltetrahydroisoquinolines which gave very



Scheme 3



Scheme 4

prominent $(M-H)^-$ ions (often the base peak), the most abundant ions in the spectra of **5-11** are due to fragments originating from the isoquiniline or the benzyl moiety. The fragmentation patterns are similar to that observed in the case of 1-benzyltetrahydroisoquinolines[7]. Ions containing the isoquinoline moiety are formed by the loss of either R_1 or R_2 followed by partial or complete aromatisation (Scheme 4). The presence of *para*-hydroxy group in the benzyl moiety results in an intense peak at *m/z* 106. RDA fragmentation is practically absent under negative ion conditions. The negative ion spectra of the benzylated derivatives give only $(M-91)^-$ ions.

Experimental Procedure

The mass spectra of the compounds (**5-11**) were recorded on a Jeol D-300 mass spectrometer having a negative ion detection unit and a JMA-2000 data system. The samples were introduced through the direct inlet system and heated to 200°. The negative ion spectra were recorded using the sodium bicarbonate technique[2]. The other ion source conditions were: electron energy, 70 eV (positive and negative); emission current, 100 μA (positive) and 300 μA (negative); and source temperature, 200°. The metastable spectra were recorded using the high voltage scan technique[3] on a Jeol 01 SG-2 mass spectrometer. The ion source conditions were: electron energy, 75 eV; emission current, 50μA; and temperature, 200°.

Table 2—Ion Abundances (%) in the Negative Ion Spectra of Compounds **5-11**

m/z	**5**	**6**	**7**	**8**	**9**	**10**	**11**
328	—	—	—	67	10	—	—
314	—	—	—	—	—	—	29
298	—	14	50	—	—	—	—
284	—	—	—	—	—	30	—
282	28	—	—	—	—	—	—
178	—	6	—	—	—	50	—
176	—	5	19	97	14	28	11
175	5	5	—	25	—	—	—
174	3	13	10	40	6	14	—
173	3	100	—	66	—	—	—
162	—	5	100	55	100	38	100
161	—	—	—	35	8	—	16
160	—	—	20	27	25	15	—
151	—	—	36	—	8	—	—
137	—	—	—	30	17	—	10
136	—	—	8	30	7	—	7
135	3	—	16	26	10	—	12
134	8	4	8	41	6	—	8
122	—	—	—	100	23	—	37
121	2	12	17	51	8	31	15
106	100	78	15	64	7	100	10

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Studies in Antifertility Agents: Part 51—Synthesis & Biological Activity of 6-Arylestradiol Derivatives†

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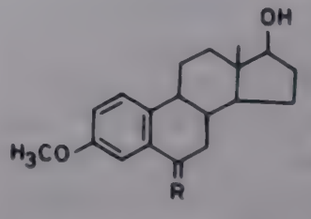
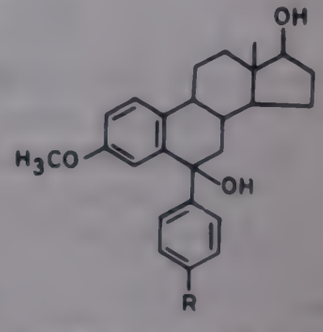
Grignard reaction of 6-oxo-estra-1,3,5(10)-triene-3,17β-diol 3-methyl ether (**3**) with arylmagnesium bromides leads to isomeric mixtures of corresponding 6-hydroxy-6-aryl compounds (**4,5**). Hydrogenolysis of these isomeric mixtures affords 6β-aryl-estra-1,3,5(10)-triene-3,17β-diol 3-methyl ethers (**10,11**) as the sole reaction products, which may also be obtained by catalytic reduction of 6-aryl-estra-1,3,5(10),6-tetraene-3,17β-diol 3-methyl ether (**6**). Stereochemical assignments have been made on the basis of chemical evidences, PMR and CMR studies. Compounds thus synthesized are 6β-phenyl-estra-1,3,5(10)-triene-3,17β-diol 3-methyl ether (**10**), 6-(*p*-hydroxyphenyl)-estra-1,3,5(10),6-tetraene-3,17β-diol 3-methyl ether (**8**), 6-(*p*-(2-diethylaminoethoxyphenyl)-estera-1,3,5(10),6-tetraene-3,17β-diol 3-methyl ether (**9**), 6β-(*p*-hydroxyphenyl)-estra-1,3,5(10)-triene-3,17β-diol 3-methyl ether (**11**) and 6β-(*p*-(2-diethylaminoethoxyphenyl)-estra-1,3,5(10)-triene-3,17β-diol 3-methyl ether (**12**). Compounds **7-12** elicit poor binding affinity for estradiol receptors, weak estrogenicity, insignificant antiestrogenicity and are ineffective in preventing implantation in rats upto 10 mg/kg dose.

Although a precise mechanism of antiestrogen action of non-steroidal antiestogens is not clearly understood, these compounds, in gneral, have a *t*-aminoethoxyphenyl moiety[1]. However, the effect of incorporation of such a basic aryl moiety in steroidal estrogens has not been studied. Some of the aminoalkyl ether derivatives of estradiol show reduced estrogenicity and antigonadotrophic activity[2]. We report herein the syntheses, stereochemical assignments, relative binding affinities (RBA) for estradiol-17β receptors, uterotrophic/antiuterotrophic and antiimplantation activities of 6β-aryl-estra-1,3,5(10)-trinene-3,17β-diol 3-methyl ethers and corresponding estra-1,3,5(10),6-tetraene compounds.

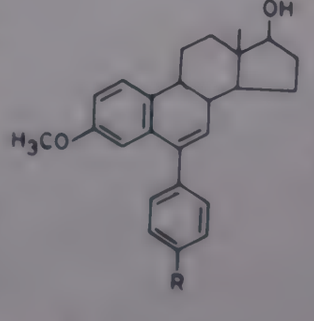
In the Grignard reaction of 6-oxo-estra-1,3,5(10)-triene-3,17β-diol 3-methyl ether[3] (**3**) with *p*-benzyloxyphenylmagnesium bromide, when the reaction mixture was decomposed with ammonium chloride, an isomeric mixture of 6-hydroxy-6-(*p*-benzyloxyphenyl)-estra-1,3,5(10)-triene-3,17β-diol 3-methyl ethers (**5a** and **5b**) was obtained. This mixture could be separated into the **5a** and **5b** by careful PTLC. Similarly the Grignard reaction of **3** with phenylmagnesium bromide led to a mixture of **4a** and **4b**. No attempts were made to separate the components, instead the mixture was converted into the tetraene[4] (**6**) Surprisingly, hydrogenolysis of **5a** or **5b**, produced exclusively 6β-aryl estrane derivative **11**, which could be alternatively prepared by acid-catalysed dehydration of **5a** and **5b** to the corresponding tetraene (**7**) followed by catalytic hydrogenation. Similarly, catalytic hydrogenation of **6** gave **10**. Catalytic hydrogenation of **7** in the presence of diethylamine resulted in the formation of the phenolic tetraene (**8**) which on



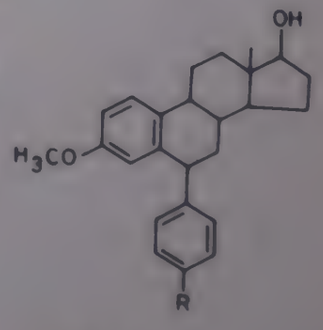
1 : R = H, H
2 : R = H, α-OH
3 : R = O



4a : R = H, 6α-OH, 6β-Ar
4b : R = H, 6β-OH, 6α-Ar
5a : R = $OCH_2C_6H_5$, 6α-OH, 6β-Ar
5b : R = $OCH_2C_6H_5$, 6β-OH, 6α-Ar



6 : R = H
7 : R = $OCH_2C_6H_5$
8 : R = OH
9 : R = OCH_2CH_2N



10 : R = H
11 : R = OH
12 : R = OCH_2CH_2N

†CDRI Communication No. 3765

alkylation with diethylaminoethyl chloride gave the basic ether (**9**). Similarly, alkylation of **11** gave the alkyl ether (**12**).

Stereochemical assignment at C-6 in isomeric **5a** and **5b** was made on the basis of chemical reactions and PMR studies. In the 6-oxo cholestane series, the intermediate OMg complex in the Grignard reaction adopts α-configuration[5] as the β-face of the steroid molecule is sterically crowded, thus forcing the alkyl/aryl substituent to attain a β-orientation. However, a study of the Dreiding model of the 6-oxo-estrane series suggests that a planar aromatic ring and lack of C-10 methyl offer comparatively less steric hindrance. Accordingly isomeric mixtures of **4a**, **4b** and **5a**, **5b** (70:30) are formed in the reaction.

A facile (within 15 min) acid-catalysed dehydration of isomer **5a** has been observed in the PMR probe itself in $CDCl_3$ containing traces of phosgene as impurity. Under a similar situation **5b** underwent dehydration only in 3 hr. This difference in dehydration rates is understandable as the 6α-OH in **5a**, which is sterically less hindered as compared to 6β-OH in **5b**, is prone to facile protonation and subsequent dehydration.

In the PMR spectra of **2**, **1** and **10**, 4-CH protons appear at δ 7.15, 6.62 and 6.45 respectively. This relatively downfield chemical shift (δ 7.15) for **2** is due to 6α-OH which is peri-planar to H-4. A comparison of chemical shifts of 4-C*H* in the isomeric alcohols **5a** and **5b** shows a relative downfield shift (δ 6.92) in **5a** (which is closer to that in **2**), as compared to that (δ 6.52) in **5b**, thus supporting the earlier assignment.

In the CMR spectra of **5a** and **5b** the C-8 carbons appear at δ 37.04 and 36.05 respectively. This upfield shift of C-8 in **5b** is likely due to 1,3-diaxial interaction with 6β-OH, thus confirming that major isomer **5a** has 6β-aryl stereochemistry.

The trienes obtained on catalytic hydrogenation of **6** and **7** have been assigned 6β-aryl geometry. It is conceivable that **6** and **7** approach the catalyst from less hindred α-face resulting into 6β-aryl product. Since **5a** and **5b** on hydrogenolysis under slightly basic conditions, afford exclusively **11**, it is presumed that the transient diaryl carbonium ion picks up hydrogen from less hindred α-face. This assignment is further confirmed by PMR studies.

It is reported[6,7] that in estranes, 6β-H and not 6α-H experiences long range coupling with H-4 and appears as a broad triplet (J=8.9 Hz). Thus in 6β-hydroxyestradiol, 6α-H forms a narrow triplet (J = 2.5 Hz), whereas in 6α-hydroxyestradiol 6β-H forms a broad triplet (J=9 Hz). In the present study C-6 proton in **8-10** in the 400 MHz PMR appears as a narrow triplet (J = 2-2.5 Hz) thus showing the absence of 6β-proton and confirming 6β-aryl stereochemistry.

Biochemical and biological activities

Relative binding affinities for estradiol receptors of **7-12** were determined as reported earlier[8] and are given in Table 1. Uterotrophic and antiuterotrophic activities in immature rat uterus following procedures reported earlier are also given in Table 1. Antiimplantation activity data of **7-12** are given in Table 1. It can be seen from Table 1 that **7-12** exhibit poor receptor binding, weak estrogenicity/antiestrogenicity and are ineffective in preventing implantation in rats upto a dose of 10 mg/kg. Compound (**9**) was tested for antiimplantation activity only at 1.5 mg/kg and found ineffective.

Experimental Procedure

Melting points were taken in a sulphuric acid bath and are uncorrected. IR spectra were recorded in KBr on Perkin-Elmer 157 and 133 spectrophotometers (ν_{max} in cm^{-1}). The high resolution (400 MHz) PMR spectra were recorded on a Bruker WM-400 NMR spectrometer equipped with ASPECT-2000 computer, using a $^{13}C/^{1}H$ dual probe head; 0.04 *M* solution in 5 mm tube with TMS as a reference. The ^{13}C-broad band (BB), single-frequency off-resonance decoupled (SFORD) and distortionless enhancement by polarization transformation (DEPT)[9] NMR spectra were run at 100-57 MHz using 0.1 *M* solution. Mass spectra were taken on a JEOL-JMS D300 instrument operating at 70 eV.

6-Phenyl-estra-1,3,5(10),6-*tetraene*-3,17β-*diol*-3-*methyl ether* (**6**)

To a stirred solution of phenylmagnesium bromide (4 mol), a solution of 6-oxo-estradiol 3-methyl ether (1 g, 0.003 mol) in dry THF (30 ml) was added dropwise at room temperature and further stirred for 2 hr. The reaction mixture was decomposed with dil HCl and extracted with ether washed with water, dried Na_2SO_4 and concentrated. The oily residue obtained was purified over a silica gel column using hexane-benzene to give **6** (0.8 g, 66.6%) as an oil; PMR ($CDCl_3$): δ 0.75 (*s*, 3H, 18 CH_3), 3.5 (*s*, 3H, OCH_3), 5.9 (*bs*, 1H, 7 CH), 6.5-7.4 (*m*, 8H, ArH); MS: *m/z* 360 (M^+) (Found: C, 83.0; H, 7.5. $C_{25}H_{28}O_2$ requires C, 83.3; H, 7.7%).

6-Phenyl-estra-1,3,5(10)-*triene*-3,17β-*diol* 3-*methyl ether* (**10**)

A solution of **6** (0.25 g) was hydrogenated over Raney-nickel catalyst (0.20 g) in methanol (ml) at 50 psi for 6 hr. The catalyst was filtered off, the filtrate concentrated in vacuo on the residual oil crystallised from benzene-hexane to afford **10** as colourless crystals, yield 0.2 g (80%), m.p. 184°; PMR ($CDCl_3$): δ 0.6 (*s*, 3H, CH_3), 0.7-2.3 (*m*, 13H, CH_2 and CH), 3.6 (*s*, 3H, OCH_3), 4.25 (*t*, 1H, 6CH, J=2.5-3 Hz), 6.44-

Table 1—Biological Data of Various Compounds

Compd	RBA rat uterine cytoplasmic estrogen receptor (%) [Mean ± SEM (n)]	Uterotrophic and antiuterotrophic activity in immature rat uterus			Antiimplantation activity in rats at dose 10 mg/kg
		Dose (μg)	Uterotrophic activity [uterine weight Mean ± SEM (n)]	Antiuterotrophic activity [uterine weight Mean ± SEM(n)]	
Estradiol 17β	100	—	—	—	—
7	Not detectable[a]	Control	9.4 ± 1.0 (5)	9.7 ± 0.6 (6)	Nil
8	1.14 ± 0.07 (3)	0.1	7.5 ± 0.8 (4)	—	
		1.0	6.6 ± 0.8 (5)	—	
		10.0	8.4 ± 0.6 (5)	52.0 ± 5.5 (6)	
		50.0	9.5 ± 0.6 (4)	33.0 ± 6.2 (6)	
		100.0	15.2 ± 1.1 (5)	42.2 ± 2.6 (6)	
		E_2-17β 0.5μg		47.3 ± 2.2 (6)	
9	0.045 + 0.013 (3)	Control	11.2 ± 1.6 (5)	10.0 ± 0.6 (6)	Nil (1.5 mg/kg)
		0.1	11.0 ± 0.9 (5)	—	
		1.0	9.2 ± 0.7 (5)	—	
		10.0	9.8 ± 1.0 (5)	36.2 ± 2.7 (6)	
		50.0	9.4 ± 0.5 (5)	38.0 ± 1.4 (6)	
		100.0	9.6 ± 1.0 (5)	40.0 ± 1.8 (5)	
		E_2-17β (0.5 μg)		41.8 ± 2.8 (5)	
10	Not detectable[b]	—	—	—	—
11	0.063 ± 0.018 (4)	Control	9.2 ± 0.4 (5)	9.0 ± 0.4 (6)	Nil
		0.1	7.2 ± 0.6 (5)	—	
		1.0	8.8 ± 0.6 (5)	—	
		10.0	7.8 ± 0.6 (5)	49.2 ± 3.3 (6)	
		50.0	9.8 ± 1.0 (5)	41.3 ± 2.8 (6)	
		100.0	13.2 ± 1.6 (5)	41.7 ± 2.8 (6)	
		E_2-17β (0.5 μg)		38.0 ± 2.3 (6)	
12	0.30 ± 0.07 (3)	Control	7.8 ± 0.2 (5)	7.8 ± 0.3 (6)	
		0.1	7.0 ± 0.5 (4)	—	
		1.0	8.3 ± 1.0 (4)	—	
		10.0	8.8 ± 0.8 (5)	39.7 ± 2.8 (6)	
		50.0	9.0 ± 0.8 (4)	43.7 ± 2.2 (6)	
		100.0	12.3 ± 0.7 (4)	29.5 ± 3.1 (5)	
		E_2-17β (0.5 μg)		38.0 ± 3.1 (5) 41.8 ± 2.8 (5)	

a & b 33 and 43% inhibition at 100 μM concentration respectively.

6.45 (*d*, 1H, 4CH, J = 2.8 Hz), 6.78 (*dd*, 1H, 2CH, $J_{1,2}$ = 8.8 Hz, $J_{2,4}$ = 2.8 Hz), 7.2 (*d*, 1H, 1CH, J = 8 Hz), 7.3-7.4 (*m*, 5H, Ar*H*); MS: *m/z* 374 (M^+) (Found: C, 83.6; H, 7.2. $C_{25}H_{30}O_2$ requires C, 83.8; H, 7.0%).

6β-(p-Benzyloxyphenyl)-6α-hydroxy-estera-1,3,5(10)-triene-3,17β-diol 3-methyl ether (**5a**) *and 6α-(p-benzyloxyphenyl)-6β-hydroxy-estra-1,3,5(10)-triene-3,17β-diol 3-methyl ether* (**5b**)

To a refluxing mixture of *p*-benzyloxybromobenzene (6 g, 0.023 mol) and dry magnesium (2.0 g, 0.08 mol) in dry ether (50 ml), 2 to 3 drops of dibromoethane were added to initiate the reaction. Vigorous reaction took place. After 1½ hr, 6-oxo-estradiol 3-methyl ether (**3**, 1 g, 0.003 mol) in dry THF (20 ml) was added dropwise. Stirring was continued for 4 hr at room temperature, the reaction mixture decomposed with aq. NH_4Cl, extracted with ether, organic layer washed with water, dried (Na_2SO_4) and concentrated. The residual viscous oil on column chromatography over silica gel using hexane-benzene gave a mixture of **5a** and **5b**, which were separated on

silica gel PTLC (tripple run) in 10% ethyl acetate-benzene. **5a**: m.p. 86-89°; PMR (acetone-d_6): δ 0.6 (*s*, 3H, 18-CH_3), 0.85-0.95 (*m*, 1H, 14-CH), 1.9-2.1 (*m*, 5H, 12-CH_2, 8-CH, 7-CH_2), 2.25-2.4 (*m*, 1H, 9-CH), 3.7 (*s*, 3H, OCH_3), 5.1 (*s*, 2H, $-OCH_2-$), 6.81-6.83 (*dd*, $J_{1,2}=8.8$ Hz, $J_{2,4}=2.4$ Hz, 1H, 2-CH), 6.87-6.89 (*d*, $J_{2',3'\text{ and }4',5'}=8.8$ Hz, 2H, 3'-CH and 5'-CH), 6.91-6.92 (*d*, $J_{2,4}=2.8$ Hz, 1H, 4-CH), 7.09-7.11 (*d*, $J=8.8$, Hz, 2H, 2'-CH and 4'-CH), 7.31-7.33 (*d*, $J=6.8$Hz, 2H, Ar*H*), 7.38-7.39 (*t*, $J=6.8$ Hz, 1H, 4''-CH), 7.46-7.48 (*d*, $J=8.0$ Hz, 2H, 3''-CH and 5''-CH), MS: *m/z* 484 (M^+); $[\alpha]_D^{28}+10.52°$ (Found: C, 79.5; H, 7.3. $C_{32}H_{36}O_4$ requires C, 79.7; H, 7.4%), **5b**: m.p. 84-86°; PMR acetone-d_6): δ 0.8·(*s*, 3H, 18-CH_3), 3.6 (*s*, 3H, OCH_3), 5.1 (*s*, 2H, OCH_2-), 6.46 (*d*, $J_{2,4}=2$ Hz, 1H, 4-CH), 6.76-6.78 (*d*, $J_{1,2}=8$ Hz, 1H, 2-CH), 6.91-6.93 (*d*, $J=8.8$ Hz, 2H, 3'-CH and 5'-CH), 7.28-7.48 (*m*, 8H, Ar*H*); MS: *m/z* 484; $[\alpha]_D^{28}-8.9°$ (Found: C, 79.9; H, 7.4. $C_{32}H_{36}O_4$ requires C, 79.7; H, 7.4%).

*6-(p-Benzyloxyphenyl)-estra-*1,3,5(10),6-*tetraene-*3,17*β-diol* 3-*methyl ether* (**7**)

A mixture of **5a** and **5b** (0.5 g) was refluxed with conc. HCl (0.5 ml) in methanol (50 ml) for 30 min. Methanol was removed, water added, extracted with ether, the organic layer washed with water, dried (Na_2SO_4) and concentrated to give **7**, which crystallised from benzene-hexane, m.p. 85-87°; IR (KBr): 1600 (aromatic), 2900 cm^{-1} (CH_2 stretching); PMR ($CDCl_3$): δ 0.75 (*s*, 3H, 18-CH_3), 3.52 (*s*, 3H, OCH_3), 4.9 (*s*, 2H, $-CH_2-C_6H_5$), 6.4-7.3 (*m*, 12H, Ar*H*); MS: (*m/z* 466 (M^+) (Found: C, 81.9; H, 7.5. $C_{32}H_{34}O_3$ requires C, 82.3; H, 7.2%).

*6-(p-Hydroxyphenyl)-estra-*1,3,5(10),6-*tetraene-*3,17*β-diol* 3-*methyl ether* (**8**)

7 (0.3 g) in methanol (50 ml) was hydrogenated at room temperature and pressure in the presence of Raney nickel catalyst (0.3 g) and a drop of diethylamine for 2 hr. Catalyst was filtered off, the filtrate concentrated *in vacuo* and the residual oil crystallised from benzne-hexane to give **8** (0.205 g), m.p. 143-45°; PMR ($CDCl_3$): δ 0.8 (*s*, 3H, 18-CH_3), 1.25-2.5 (*m*, 10H, methylenes and methines), 3.75 (*s*, 3H, OCH_3), 4.8 (*bs*, 1H, 17-CH), 5.98 (*d*, 1H, 7-CH), 6.6-7.9 (*m*, 7H, Ar*H*); MS: *m/z* 376 (M^+); $[\alpha]_D^{28}+16.5°$ (Found: C, 79.6; H, 7.4. $C_{25}H_{28}O_3$ requires C, 79.8; H, 7.4%).

*6-(p-Hydroxy)phenyl-estra-*1,3,5(10)-*triene*,-3,17*β-diol* 3-*methyl ether hydrochloride* (**11**)

7 (0.5 g) on hydrogenation in the presence of Raney nickel catalyst (0.5 g) in methanol (50 ml) at 50 psi for 6 hr gave on usual work up **11** (0.42 g) which crystallised from benzene-hexane, m.p. 211°; PMR (DMSO-d_6): δ0.6 (*s*, 3H, 18-CH_3), 3.4 (*s*, 3H, OCH_3), 4.1 (narrow *t*, $J=2.5$ Hz, 1H, 6-CH), 6.32 (*d*, $J_{2,4}=2.4$ Hz, 1H, 4-CH), 6.62-6.77 (*m*, 5H, Ar*H*), 7.25-7.25 (*d*, $J_{1,2}=8.8$ Hz, 1H, 1-CH); $[\alpha]_D^{28}+21.6°$ (Found: C, 79.5; H, 8.0. $C_{25}H_{29}O_3$ requires C, 79.3; H, 7.6%).

*6β-[p-(2-Diethylaminoethoxy)]phenyl-estra-*1,3,5(10),6-*tetraene-*3,17*β-diol* 3-*methyl ether hydrochloride* (**9**)

A mixture of **4** (0.5 g, 0.0013 mol), diethylaminoethyl chloride (0.5 g, 2.9 mol), anhydrous K_2CO_3 (2 g) in dry DMSO (25 ml) was stirred for 12 hr at room temperature. The reaction mixture was poured into water, extracted with ether, washed with water, dried (Na_2SO_4), concentrated and the oily residue filtered through basic alumina column. It was converted into hydrochloride salt, which crystallised from dry methanol-ether, to give **9**. HCl (0.6 g), m.p. 105-8°; PMR ($CDCl_3$): δ 0.8 (*s*, 3H, 18-CH_3), 4.01-4.17 (*m*, 2H, OCH_2), 6.61-7.25 (*m*, 7H, Ar*H*); $[\alpha]_D^{28}+7.9°$; MS: *m/z* 511 (M^+) (Found: C, 77.9; H, 8.5; N, 3.2. $C_{31}H_{42}NO_3Cl$ requires C, 78.3; H, 8.7; N, 2.9%).

*6β-[-p-(2-Diethylaminoethoxy)phenyl]estra-*1,3,5(10)-*triene-*3,17*β-diol* 3-*methyl ether hydrochloride* (**12**)

A mixture of **9** (0.4 g, 0.001 mol), diethylaminoethyl chloride hydrochloride (0.4 g, 0.0023 mol), anhydrous K_2CO_3 (2 g) in dry acetone (50 ml) was refluxed for 72 hr. Acetone was distilled off, water added, extracted with ether, the ether extract washed with water, dried (Na_2SO_4) and concentrated. The oil thus obtained was converted into its hydrochloride salt, what crystallised from methanol-ether to give colourless crystalline **12**, HCl (0.4 g), m.p. 190°; PMR ($CDCl_3$): δ 0.69 (*s*, 3H, 18-CH_3), 3.7 (*s*, 3H, OCH_3), 4.2 (*st*, $J=2.5$ Hz, 1H, 6-CH), 4.5 (*s*, 2H, $O-CH_2-$), 6.45 (*d*, $J=2.4$ Hz, 1H, 4-CH), 6.8 (*d*, $J=8.8$ Hz, 3H, Ar*H*), 6.95 (*d*, $J=8.8$ Hz, 2H, Ar*H*),7.3 (*d*, $J=8.8$ Hz, 1H, Ar*H*); $[\alpha]_D^{28}+16.5$ (Found: C, 71.7; H, 9.0; N, 2.4. $C_{31}H_{44}O_3NCl$ requires C, 72.4; H, 8.4; N, 2.7%).

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Notes

Synthesis of 3-Substituted 7-Hydroxy-8-arylazocoumarins

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Condensation of resorcinol with conjugated enol ethers in the presence of sodium ethoxide followed by cyclisation of the resulting compounds *in situ* with hydrochloric acid affords the 3-substituted 7-hydroxycoumarins (II) which undergo coupling reaction with suitable aryldiazonium salts to furnish the title compounds (III). The monoazo compounds (III) have been applied on polyamide and polyester as disperse dyes.

In search of useful heterocyclic azo compounds, certain coumarin derivatives have been examined in our laboratory as coupling components. We report here the synthesis of 3-substituted 7-hydroxy-8-arylazocoumarins (III). The condensation of conjugated enol ethers, diethyl ethoxymethylenemalonic ester (EMME) and diethyl ethoxymethylenecyanoacetate (EMCA) with resorcinol in abs. ethanol in the presence of sodium ethoxide[1,2] and subsequent cyclization with hydrochloric acid gave 3-carbethoxy-7-hydroxycoumarin (IIa) and 3-cyano-7-hydroxycoumarin (IIb), respectively. The alkaline hydrolysis of IIa and subsequent cyclization with hydrochloric acid afforded 3-carboxy-7-hydroxycoumarin (IIc). The 7-hydroxycoumarins (IIa-c) were buff coloured solids soluble in water and their solutions exhibited blue fluorescence.

Some hydroxycoumarins have been reported earlier as coupling components[3]. It was therefore expected that aryldiazonium salts when coupled with 3-substituted 7-hydroxycoumarin (IIa-c), monoazo compounds would result, coupling taking place at 8-position of the coumarin and simultaneous ring opening occurring under alkaline condition. However, in excess aryldiazonium salts, the second coupling is expected to take place at 6-position under more basic condition resulting in bisazo compounds. Both monoazo and bisazo compounds would undergo cyclization to monoazocoumarins (III) and bisazocoumarins respectively. The formation of 8-monoarylazo and 6, 8-bisarylazo derivatives of 7-hydroxycoumarin was observed by Rangaswami and Seshadri[4].

Aromatic amines were diazotised and coupled at controlled *p*H with equimolar amounts of IIa-c when only monoazo compounds resulted in as confirmed by TLC and elemental analyses. The selective formation of 8-arylazocompounds (III) in high yields (88-100%; Table 1) and their purity are important because such compounds are useful as brilliant yellow to red disperse dyes. The characterization data of III are given in Table 1.

Dyeing properties

The highly coloured 3-substituted 7-hydroxy-8-arylazocoumarins (III) were applied as disperse dyes on polyester and polyamide fibres. Most of the compounds showed good pick-up and fastness. The shades were brilliant yellow to red. The exhaustion of the dyes was found to be better in the case of polyamide as compared to polyester fibres. The light fastness is better on polyester (3-6) than that on polyamide (3-4). The dyes III_4, III_8-III_{12}, III_{15} and III_{16} showed

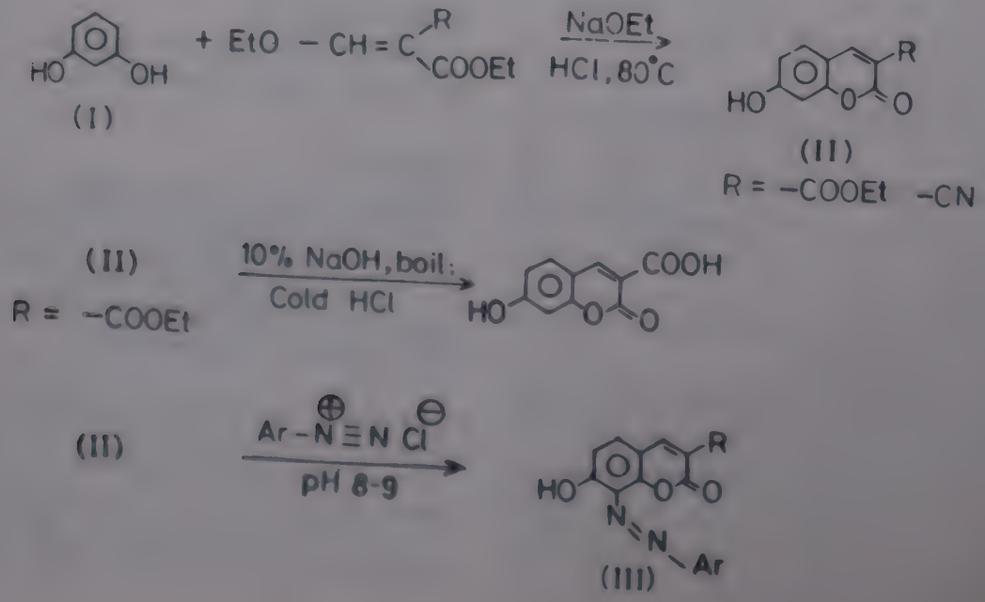

Table 1—Characterization Data of 3-Substituted 7-Hydroxy-8-arylazocoumarins (III)

Compd*	R^1	R^2	R^3	R^4	Yield (%)	m.p.† °C	Mol. formula	UV (visible)	
								λ_{max} (nm)	log ε
				R = −COOEt					
III_1	OCH_3	Cl	H	H	89	236	$C_{19}H_{15}N_2O_6Cl$	465	4.72
III_2	CH_3	NO_2	H	H	93	208-9	$C_{19}H_{15}N_3O_7$	415	4.69
III_3	H	NO_2	H	H	94	218	$C_{18}H_{13}N_3O_7$	505	4.76
III_4	Cl	NO_2	H	H	96	210	$C_{18}H_{12}N_3O_7Cl$	435	4.53
III_5	NO_2	NO_2	H	H	99	224-25	$C_{18}H_{12}B_4O_9$	440	4.52
III_6	NO_2	NO_2	H	Br	98	238-39	$C_{18}H_{11}N_4O_9Br$	430	4.39
				R = −COOH					
III_7	Cl	NO_2	H	H	94	228-29	$C_{16}H_8N_3O_7Cl$	560	4.74
III_8	CN	NO_2	H	H	99	237-38	$C_{17}H_8N_4O_7$	570	4.46
III_9	SO_2CH_3	NO_2	H	H	99	234-35	$C_{17}H_{11}N_3O_9S$	560	4.40
III_{10}	NO_2	NO_2	H	H	100	226-27	$C_{16}H_8N_4O_9$	520	4.37
III_{11}	Cl	NO_2	H	Cl	97	212-14	$C_{16}H_7N_3O_7Cl_2$	420	4.39
				R = −CN					
III_{12}	H	CH_3	H	H	90	221-22	$C_{17}H_{11}N_3O_3$	435	4.65
III_{13}	Cl	H	Cl	H	88	231-33	$C_{16}H_7N_3O_3Cl_2$	410	4.35
III_{14}	H	NO_2	H	H	93	226-28	$C_{16}H_8N_4O_5$	430	4.35
III_{15}	Cl	NO_2	H	H	95	217-18	$C_{16}H_7N_4O_5Cl$	575	4.76
III_{16}	NO_2	NO_2	H	H	98	214-15	$C_{16}H_7N_5O_7$	530	4.52
III_{17}	NO_2	NO_2	H	Br	98	214-16	$C_{16}H_6N_5O_7Br$	485	4.47

*All the compounds give satisfactory elemental analyses.
†Melting points are uncorrected.

excellent fastness on polyester. The sublimation fastness of all the dyes was good (3-4). The dyes derived from IIc were found to be superior to those derived from IIa and IIb.

3-Carbethoxy- and 3-cyano-7-hydroxycoumarins (IIa and IIb) were prepared by known procedures[1,2].

3-*Carboxy-7-hydroxycoumarin* (*IIc*)

Sodium hydroxide solution (10%) (25 ml) was added to 3-carbethoxy-7-hydroxycoumarin (IIa; 2.34 g, 0.01 mol) and the mixture gently boiled for half an hr to give a clear solution. After the completion of hydrolysis, the reaction mixture was boiled for 5 min with a pinch of activated charcoal and filtered hot. The filtrate was run into excess of cold 1:1 hydrochloric acid. The bulky precipitate separated after prolonged cooling was filtered, washed free of acid and dried, yield = 1.94 g (94%), m.p. 262° (d).

3-*Substituted 7-hydroxy-8-arylazocoumarins*(*III*): *General Prqcedure*

A solution of II (0.01 mol) in aq. sodium carbonate (30%) was cooled to 0° and a clear diazonium salt solution, obtained by the diazotisation of an appropriate aromatic amine (0.01 mol), added to it slowly at 0-5° with stirring during 45-60 min. The *p*H of the reaction mixture was maintained at 8-9 and finally adjusted to 8.5. The reaction mixture was stirred at 0-5° for 5-8 hr. At the end of the coupling reaction, the mixture was acidified with conc. hydrochloric acid to *p*H 2 and heated at 80° for 45min. The resultant azo dye was filtered, washed free of acid and dried, yield 88-100% (Table 1).

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Synthesis of Some New 3-Methylisocoumarins

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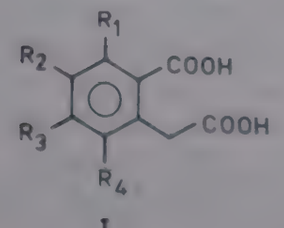
Condensation of 2-carboxyphenylacetic acid(I) with acetic anhydride in the presence of pyridine at room temperature furnishes the corresponding 4-acetylisochroman-1,3-diones (II). At boiling water-bath temperature, however, 4-carboxy-3-methylisocoumarins (III) with small amounts of napthoisocoumarin (IVa, b, c) are obtained. Compounds II on treatment with 80% H_2SO_4 undergo rearrangement to give III in quantitative yields. The latter (III) on decarboxylation furnish the corresponding 3-methylisocoumarins(V), while on hydrolysis ketones VI are obtained. The latter compounds (VI) on reduction with sodium borohydride afford the dihydro derivatives (VII). 3-Methylisocoumarins (V) when refluxed with ethanolic ammonia furnish the isoquinolones (VIII).

The earlier synthesis[1-3] of 3-alkylisocoumarins involve the condensation of homophthalic acids or their anhydrides with acetic anhydride or propionic anhydride in the presence of pyridine as catalyst. Adopting this procedure, we have now carried out the synthesis of some new 3-methylisocoumarins starting from 2-carboxyphenylacetic acids (Ia-e)[4-7]. These acids on condensation with acetic anhydride in the presence of dry pyridine at room temperature furnished the corresponding 4-acetylisochroman-1,3-diones (IIa-e), which underwent rearrangement in the presence of 80% H_2SO_4 to give the corresponding 4-carboxy-3-methylisocoumarins (IIIa-e) (Table 1). However, a similar condensation of I with acetic anhydride when carried out on a boiling water-bath produced III along with small amounts of naphthoisocoumarins (IVa, b, c). We could not isolate the naphthoisocoumarins in the case of Ic and Id.

The isocoumarins (IIIa-e) were decarboxylated in methanolic solution (0.3-0.5g III in 5-10 ml MeOH) under reflux (12 hr) as well as by heating them above their melting points to give the corresponding 3-methylisocoumarins (Va-e; Table 1). Treatment of IIIa-e with NaOH (10%) brought about opening of the lactone ring to furnish the corresponding methyl ketones (VIa-e; Table 1) which were also obtained by the action of NaOH on IIa-e. These methyl ketones (VI) were cyclodehydrated to the corresponding isocoumarins (Va-e) by keeping with 90% sulphuric acid. They were also reduced with sodium borohydride to the corresponding 3,4-dihydro derivatives (VIIa-e; Table 1) which were transformed back into the original isocoumarins (Va-e) by treatment with N-bromosuccinimide. The isocoumarins Va-e were characterised as isoquinolone derivatives (VIIIa-e), prepared by refluxing V with ethanolic ammonia.

The structures assigned were found compatible with elemental analyses, UV, IR and PMR data.



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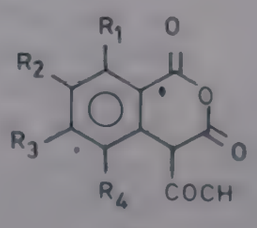
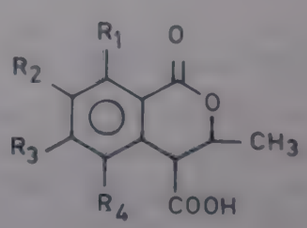


II



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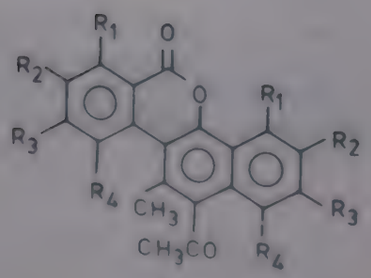
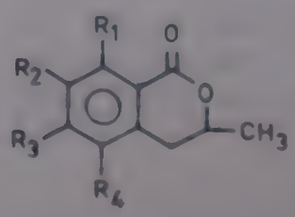


IV (a,b,e)



V

a, $R_2 = R_2 = OMe$, $R_1 = R_3 = H$
b, $R_3 = R_4 = OMe$, $R_1 = R_2 = H$
c, $R_2 = OMe$; $R_3 = Me$, $R_1 = R_4 = H$
d, $R_1 = Me$; $R_4 = OMe$, $R_2 = R_3 = H$
e, $R_1 = Me$; $R_4 = OMe$, $R_2 = R_3 = H$

Table 1—Characterisation Data of Various Compounds Prepared

Compound	Yield (%)	m.p. °C	Crystallised from	Mol. formula	Found (%)		(Calc.)		60 MHz PMR ($CDCl_3$) (δ, ppm)
					C	H	C	H	
IIa	58	15-6	Pet. ether	$C_{13}H_{12}O_5$	63.1	4.6	62.9	4.8	—
IIb	55	135-36	Pet. ether-C_6H_6	$C_{13}H_{12}O_6$	59.0	4.4	59.1	4.6	—
IIc	52	108-9	Pet. ether-C_6H_6	$C_{13}H_{12}O_5$	62.8	4.7	62.9	4.8	—
IId	56	111-12	Dioxane	$C_{13}H_{12}O_5$	62.7	4.8	62.9	4.8	—
IIe	50	177-78	$CHCl_3$-pet. ether	$C_{13}H_{12}O_6$	58.8	4.5	59.1	4.6	—
IIIa	60	197-98	C_6H_6	$C_{13}H_{12}O_5$	62.9	5.00	62.9	4.8	—
IIIb	56	211-12	EtOAc	$C_{13}H_{12}O_6$	59.1	4.6	59.1	4.6	—
IIIc	64	200-201	C_6H_6	$C_{13}H_{12}O_5$	62.9	4.8	62.9	4.8	—
IIId	60	188-89	MeOH	$C_{13}H_{12}O_5$	62.6	4.7	62.9	4.8	—
IIIe	54	240-41	MeOH	$C_{13}H_{12}O_6$	59.0	4.4	59.1	4.6	—
Va	62	144-45	C_6H_6-pet. ether	$C_{12}H_{12}O_3$	70.0	5.8	70.6	5.9	2.27(3H, *s*, 3-CH_3), 2.43(3H, *s*, 7-CH_3), 3.92(3H, *s*, 5-OCH_3), 6.57(1H, *s*, H-4) 6.95(1H, *s*, H-6), 7.65(1H, *s*, H-8),
Vb	58	152-53	C_6H_6	$C_{12}H_{12}O_4$	65.5	5.4	65.5	5.5	2.4(3H, *s*, 3-CH_3), 3.98(6H, *s*, 5- and 7-OCH_3) 6.6(1H, *s*, H-4), 7.0(1H, *s*, H-6), 7.65(1H, *s*, H-8),
Vc	65	139-40	EtOAc	$C_{12}H_{12}O_3$	70.6	5.8	70.6	5.9	2.35(3H, *s*, 3-CH_3), 2.5(3H, *s*, 6-CH_3), 3.89(3H, *s*, 7-OCH_3), 6.0(1H, *s*, H-4), 7.2-8.0(2H, *m*, H-5 and H-8)
Vd	62	155-56	Pet. ether	$C_{12}H_{12}O_3$	70.4	5.8	70.6	5.9	2.32(3H, *s*, 3-CH_3) 2.50(3H, *s*, 8-CH_3) 3.85(3H, *s*, 5-OCH_3) 6.42(1H, *s*, H-4) 7.0-7.9(2H, *m*, H-6 and H-7)
Ve	58	145-46	C_6H_6	$C_{12}H_{12}O_4$	65.3	5.4	65.5	5.5	2.25(3H, *s*, 3-CH_3), 3.90(6H, *s*, 5- and 6-OCH_3) 6.2(1H, *s*, H-4), 7.1-7.7(2H, *m*, H-7 and H-8)
VIa	80	174-75(2,4-DNP, 191-92)	EtOAc-pet. ether	$C_{12}H_{14}O_4$	64.1	6.2	64.1	6.3	—

—Contd.

Table 1—Characterisation Data of Various Compounds Prepared—(*Contd.*)

Compound	Yield (%)	m.p. °C	Crystallised from	Mol. formula	Found (%)		(Calc.)		60 MHz PMR ($CDCl_3$) (δ, ppm)
					C	H	C	H	
VIb	75	110-11(2,4-DNP, 128-29)	C_6H_6	$C_{12}H_{14}O_5$	60.3	5.7	60.5	5.9	—
VIc	76	154-55(2,4-DNP, 185-86)	$CHCl_3$	$C_{12}H_{14}O_4$	64.8	6.2	64.9	6.3	—
VId	74	176-77(2,4-DNP, 190-91)	Pet. ether	$C_{12}H_{14}O_4$	64.8	6.2	64.9	6.3	—
VIe	82	170-71(2,4-DNP, 194-95)	$CHCl_3$	$C_{12}H_{14}O_5$	60.4	5.8	60.5	5.9	—
VIIa	85	128-29	$CHCl_3$-pet. ether	$C_{12}H_{14}O_3$	69.7	6.6	69.9	6.8	—
VIIb	85	127-28	C_6H_6	$C_{12}H_{14}O_4$	64.7	6.1	64.9	6.3	—
VIIc	82	117-18	$CHCl_3$	$C_{12}H_{14}O_3$	69.7	6.7	69.9	6.8	—
VIId	84	145-46	Pet. ether	$C_{12}H_{14}O_3$	69.7	6.7	69.9	6.8	—
VIIe	78	122-23	C_6H_6	$C_{12}H_{14}O_4$	64.8	6.2	64.9	6.3	—
VIIIa	60	22-23	EtOAc	$C_{12}H_{13}O_2N$	70.4	6.1	70.9	6.4	—
VIIIb	60	168-69	EtOAc	$C_{12}H_{13}O_3N$	65.4	5.7	65.7	5.9	—
VIIIc	65	157-59	C_6H_6	$C_{12}H_{13}O_2N$	70.6	6.2	70.9	6.4	—
VIIId	60	172-73	EtOAc	$C_{12}H_{13}O_2N$	70.2	5.9	70.9	6.4	—
VIIIe	55	157-58	EtOH	$C_{12}H_{13}O_3N$	65.2	5.6	65.7	5.9	—

Compounds VIIIa-e were also analysed satisfactorily for N.

4-Acetylisochroman-1,3-diones (IIa-e)

Homophthalic acid (2.0-2.5g) (Ia-e) was added in instalment to a well stirred mixture of acetic anhydride (4-7ml) and dry pyridine (4.0-6.0 ml). The acid slowly dissolved to form an yellow solution which on standing turned into a semi-solid mass. Dry ether (10.0-15.0 ml) was then added to the mixture and the reaction mixture stirred for 1-1.5 hr. The resultant solid was filtered, washed well with ether, dried and crystallised from a suitable solvent (Table 1).

4-Carboxy-3-methylisocoumarins (IIIa-e)

A mixture of I (2.0-2.5 g), acetic anhydride (5.0-8.0 ml) and dry pyridine (6.0-8.0 ml) was heated on a boiling water-bath for 2 hr, poured into crushed ice containing conc. HCl and kept overnight in a refrigerator. The sticky solid obtained was dissolved in hot benzene (A) containing a little ethanol. The supernatant aq. layer was extracted with ethyl acetate. The benzene solution and also the ethyl acetate extract were seprately and repeatedly shaken with sodium bicarbonate solution (20%, 20 ml each). The sodium bicarbonate extracts were combined, washed with benzene and acidified with conc. HCl when compound III separated out slowly as a light yellow solid and crystallised from a suitable solvent (Table 1); UV (MeOH): 255-285 and 330-350 nm.

The benzene solution (A) was washed with water, dried (Na_2SO_4) and concentrated to a small bulk which on cooling deposited white crystals of naphthoisocoumarin IVa, b or c.

Rearrangement of 4-acetylisachroman-1,3-diones (IIa-e)

Compound II (0.3-0.5 g) was added portionwise to 80% H_2SO_4 (3.0-5.0 ml) at 0-5° with shaking. The reaction mixture was kept overnight in a refrigerator, poured into crushed ice. The solid residue obtained was triturated with a saturated solution of $NaHCO_3$ and filtered. The alkaline filtrate on acidification with conc. HCl acid furnished III (Table 1). The residue obtained after sodium bicarbonate treatment was crystallised from a suitable solvent to give 3-methylisocoumarins (Va-e; Table 1).

2-Carboxybenzyl methyl ketones (VIa-e)

(i) A solution of II (0.5 g) in 10% aq. NaOH (10-15 ml) was refluxed for 2 hr on a boiling water-bath, cooled and acidified with conc. HCl to furnish VI (Table 1).

(ii) A solution of III (0.1-0.15 g) in 10% NaOH (6.0 ml) was refluxed for 2 hr , cooled and acidified with conc. HCl to give VI (Table 1).

2,4-Dinitrophenyl hydrazone drivatives of the above ketone were prepared in the usual way

Cyclodehydration of VI

Compound VI (0.2-0.21 g) was treated with 90% H_2SO_4 (1.0-1.5 ml) and kept overnight at room temperature when a dark green solution resulted in. It was poured into crushed ice and the resultant solid washed with saturated $NaHCO_3$ solution and crystallized to give V, identical (m.p., m.m.p.) with that obtained above.

3-Methyl-3,4-dihydroisocoumarins (VIIa-e)

$NaBH_4$ (0.2-0.3 g) was added portionwise to VI (0.15-0.20 g) in methanol (3.0-5.0 ml) and the reaction allowed to continue for 2-3 hr at room temperature. The reaction mixture was then acidified with conc. HCl, diluted with water and the precipitated pale yellow solid filtered, washed and crystallised from a suitable solvent to give VII (Table 1).

Conversion of VIIa-e into Va-e

A mixture of VII (0.1-0.15 g), N-bromosuccinimide (0.15-0.20 g), dry CCl_4 and benzoyl peroxide (0.01 g) was taken in a round bottom flask, kept close to a 60 watt lamp and refluxed on a water-bath for 2 hr. A further quantity of benzoyl peroxide (0.01 g) was added and refluxing continued for another 2 hr. It was then cooled and filtered to remove succinimide. The filtrate was washed with 5% aq. sodium carbonate, ice-water and dried (Na_2SO_4). Removal of CCl_4 gave a solid which was refluxed with Et_3N for 18 hr, base distilled off and the residue triturated with pet. ether (60°-80°) and crystallised from a suitable solvent to give V.

3-Methylisoquinolones (VIIIa-e)

A mixture of V (0.1-0.15 g), ethanol (5-10 ml) and ammonia (6.0-10.0 ml) was refluxed for 4-6 hr on a boiling water-bath. After the removal of ethanol, the solid residue was triturated with pet. ether and crystallised from a suitable solvent to give VIII (Table 1).

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A Facile Synthesis of Furobenzodipyrans

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5-Hydroxybergapten (**1a**) and 5-hydroxyisopimpinellin (**1b**) react with β-keto esters in the presence of ammonium acetate to form the corresponding furobenzodipyran derivatives (**3a-f** and **4a,b**).

Furocoumarins are known to possess pronounced photosensitizing activity[1-3], a broad spectrum antibacterial[4] activity, tuberculostatic[5] and molluscicidal properties[6]. The aim of the present work is to synthesize condensed furobenzodipyran derivatives (**3a-f** and **4a,b**) and to test these for biological activity.

The starting 5-hydroxy-4-methoxy-7*H*-furo[3,2-*g*][1]benzopyran-7-one (5-hydroxybergapten) (**1a**) and 5-hydroxy-4,9-dimethoxy-7*H*-furo[3,2-*g*][1]benzopyran-7-one (5-hydroxyisopimpinellin) (**1b**) were prepared, respectively by Claisen condensation of diethyl carbonate with visnaginone and khellinone.

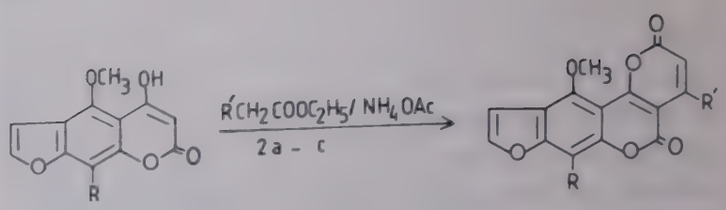
Reactions of **1a** and **1b** with β-keto esters (**2a-c**) in the presence of ammonium acetate gave the corresponding condensed compounds (**3a-f**)[7]. The structural assignment of **3a-f** was based on the PMR data. For example, the PMR spectrum of **3a** revealed two doublets at δ 7.76 & 7.26 (J = 2.6 Hz) representing the C_2- and C_3-protons, respectively. The other signals appeared at δ 7.1 (*s*, 1H, C_{11}–H), 6.53 (*q*, 1H, C_7–H), 4.6 (*s*, 3H, OCH) and 2.9 (*s*, 3H, CH_3).

The reaction of **1a** and **1b** with ethyl cyclopentanone-2-carboxylate in the presence of ammonium acetate led to the formation of the corresponding furobenzodipyran derivatives (**4a** and **4b**).

The PMR spectrum of **4a** displayed a singlet at δ 7.79 (1H, C_{12}–H), two doublets at 7.73 and 7.27 (J = 1.9 Hz, 1H each, C_2– and C_3–, protons respectively), a singlet at 4.5 (3H, OCH_3), two triplets at 3.74 and 3.18 (2H each, C_7– and C_9-protons), and a sextet at 2.42 (2H, C_8–H_5). The structure of **4b** was also supported by its PMR spectrum.

The mass spectrum of **4b** showed the molecular ion peak at *m/z* 354 as base peak and other fragments at *m/z* 289, 302, 314, 326, 339, 353, 354, 355.

Melting points are not corrected. The PMR spectra were recorded in deuterated TFA on a Bruker 200 MHz spectrophotometer and mass spectra on an MS 9-50 instrument.

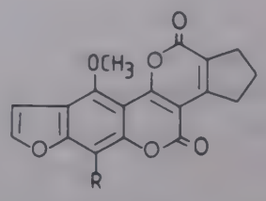


a , R = H
b , R OCH3

a , R' = COCH3
b , R' = COC6H5
c , R' = COOC2H5

3a - f

a , R = H ; R' = CH3
b , R = H ; R' = C6H5
c , R = H ; R' = OH
d , R = OCH3 ; R' = CH3
e , R = OCH3 ; R' = C6H5
f , R = OCH3 ; R' = OH



4
a , R = H
b , R = OCH3

Table 1—Furobenzodipyran Derivatives (**3a-f** and **4a,b**)

Compd	m.p. °C crystallised from	Mol. formula	Calc. (Found) %	
			C	H
3a	250 (chloroform)	$C_{16}H_{10}O_6$	64.42 (64.24)	3.35 (3.02)
3b	242 (acetone)	$C_{21}H_{12}O_6$	70.00 (69.80)	3.30 (3.10)
3c	240 (chloroform)	$C_{15}H_8O_7$	60.00 (60.34)	2.66 (2.91)
3d	295 (acetone)	$C_{17}H_{21}O_7$	62.19 (62.03)	3.6 (3.54)
3e	180 (chloroform)	$C_{22}H_{14}O_7$	67.6 (67.43)	3.58 (3.32)
3f	285 (acetic acid)	$C_{16}H_{10}O_8$	58.18 (58.36)	3.03 (3.26)
4a	250 (chloroform)	$C_{18}H_{12}O_6$	66.60 (66.87)	3.70 (3.92)
4b	275 (acetone)	$C_{19}H_{14}O_7$	64.40	3.95 (3.76)

Reaction of 5-hydroxybergapten (**1a**) *and 5-hydroxyisopimpinellin* (**1b**) *with β-keto esters*:

General procedure

A mixture of **1** (10 mmol) and **2** (15 mmol) was heated on a sand-bath at 185 C under an air

condenser. The reaction mixture was then well stirred with 4% aq. sodium carbonate (150 ml) and left overnight to remove starting material. Recrystallization from the appropriate solvent yielded the furobenzodipyran derivatives (**3a-f** and **4a,b**) (cf. Table 1), in good yields 75-95%.

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Aromatic Benzylation: Part VI—Some More Experiments on Nuclear Benzylation of 2,4-Dihydroxydesoxybenzoin & Synthesis of C-Benzylated Isoflavones

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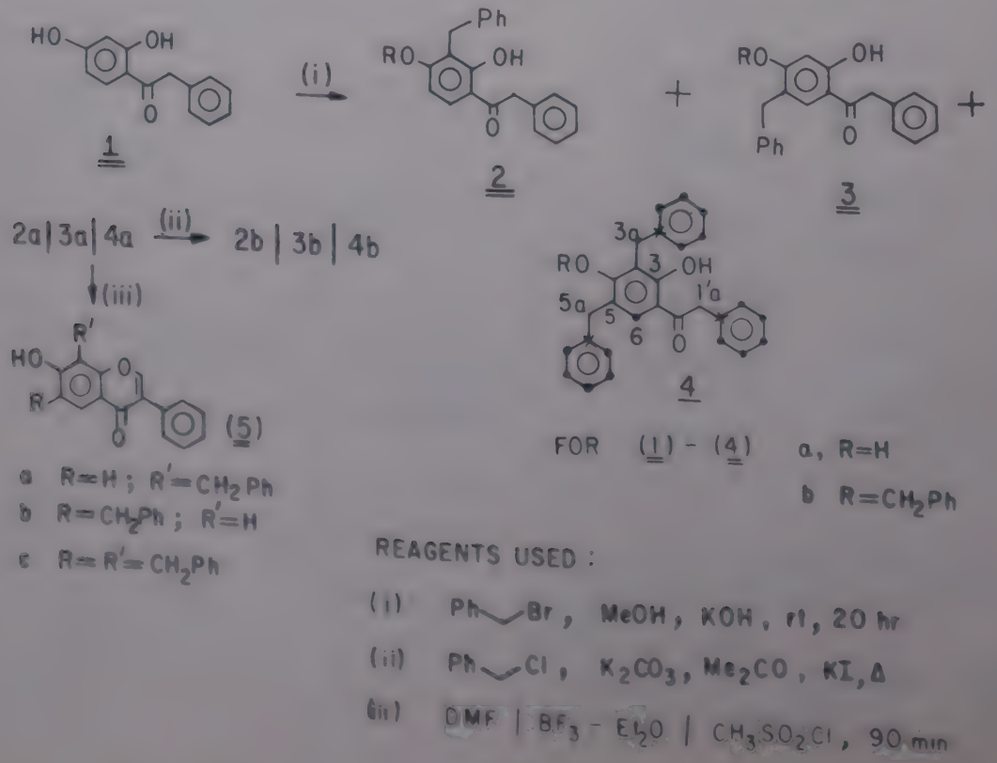
2,4-Dihydroxydesoxybenzoin (**1a**) reacts with benzyl bromide in the presence of MeOH – KOH at room temperature to give 4-benzyl ether (**1b**) (31.4% yield), 3-C-benzyl derivative (**2a**, 12.2%), 5-C-benzyl derivative (**3a**, 2.8%), 3,5-di-C-benzyl derivative (**4a**, 1.4%) and 3-C-benzyl-4-benzyl ether (**2b**, 0.7%). The desoxybenzoins **2a**, **3a** and **4a** have also been converted into the corresponding C-benzylated isoflavones (**5a**, **5b** and **5c**).

Earlier[1] in our programme on the syntheses of C-benzylated polyphenols[1-5], 2,4-dihydroxydesoxybenzoin (**1a**) was C-benzylated[1] with benzyl alcohol in the presence of BF_3-Et_2O and dioxan. The same substrate has now been reacted with benzyl bromide in the presence of methanolic potash when a complex mixture of products was obtained. From the column chromatography of this mixture five pure compounds were isolated. Two of them were identified as 4-benzyloxy-2-hydroxydesoxybenzoin (**1b**; 31.4% yield) and 3-C-benzyl-2,4-dihydroxydesoxybenzoin (**2a**; 12.2% yield) by comparison with the samples obtained earlier[1]. The other two products identified as 5-C-benzyl-2,4-dihydroxydesoxybenzoin (**3a**; 2.79% yield) and 3,5-di-C-benzyl-2,4-dihydroxydesoxybenzoin (**4a**; 1.36% yield). The compound formed in the minimum amount (0.68% yield) was assigned the structure 3-C-benzyl-4-benzyloxy-2-hydroxydesoxybenzoin (**2b**) on the basis of its PMR spectrum and direct comparison with the compound prepared unambiguously by reaction of 3-C-benzyl-2,4-dihydroxydesoxybenzoin (**2a**) with one mol of benzyl chloride in the presence of K_2CO_3 and acetone. Further, 4-benzyl ethers (**3b** and **4b**) of 5-C-benzyl- and 3,5-di-C-benzyl-2,4-dihydroxydesoxybenzoins were also prepared in the same manner.

In an earlier study[1] C-benzylated-2,4-dihydroxydesoxybenzoins were converted into the corresponding 7-acetoxy-2-methylisoflavones. These deoxybenzoins (**2a**, **3a** and **4a**) have now been converted into the corresponding 7-hydroxyisoflavones (**5a**, **5b** and **5c**) by treatment with DMF in the presence of $BF_3.Et_2O$ and methanesulphonyl chloride. The resultant C-benzylated isoflavones were characterized by the preparation of their 7-acetates and by their PMR spectra.

Unless stated otherwise, all m.ps are uncorrected; pet. ether had b.p. 60-80°; silica gel G was used for column chromatography and TLC; solvent system used for TLC were: (A) benzene-petrol (1:1), (B) benzene, (C) benzene-ethyl acetate (9:1) and (D)



benzene-ethyl acetate (3:1); R_f values refer to TLC; UV data were recorded in methanol on a Perkin-Elmer 554 spectrophotometer (λ_{max} in nm and log ε values are given in parentheses); IR spectra were recorded in KBr on a Shimadzu IR-435 spectrophotometer (ν_{max} in cm^{-1}) and PMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ using TMS as an internal standard on Perkin-Elmer R-32 (90 MHz) and JEOL FX-200 (200 MHz) instruments respectively (chemical shifts in δ, ppm).

Reaction of 2,4-*dihydroxydesoxybenzoin* (**1a**) *with benzyl bromide*

2,4-Dihydroxydesoxybenzoin[6] (**1a**; 2.2 g, 9.6 mmol) was added to an ice-cooled solution of KOH (4.0 g) in abs. MeOH (20 ml) and the resulting solution treated with benzyl bromide (5.1 g, 28.8 mmol) slowly while shaking and then left overnight at room temperature for 24 hr. The reaction mixture was diluted with ice-cold water, acidified and extracted with ether. The ethereal layer was dried (Na_2SO_4), evaporated to dryness and the residue subjected to column chromatography. Successive elution of the column with (i) pet. ether, (ii) pet. ether-benzene (19:1), (iii) pet. ether-benzene (9:1), (iv) pet. ether-benzene (8:2), (v) pet. ether-benzene (3:1), and (vi) pet. ether-benzene (1:1) gave six fractions (I-VI).

Fraction-I: It crystallized from methanol to afford 3-C-benzyl-4-benzyloxy-2-hydroxydesoxybenzoin (**2b**) as white crystals (25 mg), m.p. 97-98°; gave green ferric reaction; R_f 0.54 (solvent-A) (Found: C, 82.0; H, 6.0. $C_{28}H_{24}O_3$ requires C, 82.3; H, 5.9%); UV: 230 (4.5) and 292 (4.5); IR: 1625, 1580; 90 MHz PMR: 3.99 (*s*, 2H, $-CH_2Ph$), 4.14 (*s*, 2H, $CO-CH_2Ph$), 5.10 (*s*, 2H, $-OCH_2Ph$), 6.44 (*d*, $J=9.5$ Hz, 1H, C_5-H), 7.20-7.29 (*m*, 15H, $3\times-C_6H_5$), 7.69 (*d*, $J=9.5$ Hz, 1H, C_6-H), and 12.89 (*s*, 1H, chelated OH).

Fraction-II: It crystallized from benzene-pet. ether to yield 4-benzyloxy-2-hydroxydesoxybenzoin (**1b**) (900 mg), m.p. and m.m.p. 105-6° (lit.[7], m.p. 104-5°).

Fraction-III: It crystallized from benzene-pet. ether to afford 3,5-di-C-benzyl-2,4-dihydroxydesoxybenzoin (**4a**, 50 mg), m.p. and m.m.p. 110-12° (lit.[1], m.p. 111-12°); 50 MHz ^{13}C-NMR: 28.4, 35.9 (each *t*, C-3a and C-5a), 45.1 (*t*, C-1'a), 113.0, 114.8, 118.9, 130.9, 134.6, 139.8 (each *s*, C-1, C-3, C-5, 3 aromatic carbons marked *), 126.4-129.3 (*m*, 16 aromatic carbons marked ●), 159.1 (*s*, C-4), 162.2 (*s*, C-2) and 202.2 (*s*, C=O).

Its partial benzyl ether (**4b**) was prepared by heating with 1 mol equiv. of benzyl chloride and 4 mol equiv. of K_2CO_3 in acetone for 90 min, and crystallized from pet. ether as light yellow crystals (20 mg), m.p. 51-52°; gave green ferric reaction; R_f 0.60 (solvent-A) (Found: C, 83.9; H, 6.4. $C_{35}H_{30}O_3$ requires C, 84.3; H, 6.0%); UV: 220 (4.6) and 282 (4.41); IR: 1630, 1590, 1500; 90 MHz PMR: 3.87, 3.90 (2*s*, 4H, $2\times-CH_2Ph$), 4.10 (*s*, 2H, $-COCH_2Ph$), 4.41 (*s*, 2H, $-OCH_2Ph$), 6.97-7.21 (*bm*, 20H, $4\times-C_6H_5$), and 7.51 (*s*, 1H, C_6-H).

Fraction-IV: It crystallized from benzene-pet. ether to furnish 3-C-benzyl-2,4-dihydroxydesoxybenzoin (**2a**; 350 mg), m.p. 122-24° (lit.[1], m.p. 121-22°). Its partial benzyl ether (**2b**) was found identical with the compound obtained from fraction-I (*vide supra*).

Fraction-V: It crystallized from benzene-pet. ether to give 5-C-benzyl-2,4-dihydroxydesoxybenzoin (**3a**; 80 mg), m.p. and m.m.p. with an authentic sample 126-28° (lit.[1], m.p. 128-29°).

Its partial benzyl ether (**3b**) crystallized from ethanol as colourless crystals (20 mg), m.p. 90-92°; gave green ferric reaction; R_f 0.74 (solvent-B) (Found: C, 81.9; H, 6.3. $C_{28}H_{24}O_3$ requires C, 82.3; H, 5.9%); IR: 1620, 1600, 1550; 90 MHz PMR: 3.70 (*s*, 2H, $-CH_2Ph$), 4.04 (*s*, 2H, $-COCH_2Ph$), 5.16 (*s*, 2H, $-OCH_2Ph$), 6.61 (*s*, 1H, C_3-H), 7.30 (*s*, 10H, $2\times C_6H_5$), 7.50 (*s*, 5H, $-C_6H_5$ of ring-B), 7.73 (*s*, 1H, C_6-H), and 13.42 (*s*, 1H, chelated OH).

Fraction-VI: It crystallized from methanol to give the starting material **1a** (150 mg), m.p. and m.m.p. 114-15°.

C-Benzylated-7-hydroxyisoflavones (**5a-c**)

To a cooled solution of the desoxybenzoin (**2a**/**3a**/**4a**) (0.12 mmol) in DMF (2.5 ml) was added BF_3-Et_2O (0.3 ml) dropwise and the solution kept for 30 min at room temperature. The temperature was then raised to 60° and CH_3SO_2Cl (0.4 ml) in DMF (2.0 ml) added to it in one lot. The resulting mixture was heated on a boiling water-bath for 90 min, cooled, poured into ice-cold water, and the product collected. The characterization data of the compounds thus prepared are as follows:

8-*C-Benzyl-7-hydroxyisoflavone* (**5a**): Colourless solid from benzene-pet. ether, m.p. 166-68°; R_f 0.58 (solvent-D) (Found: C, 80.0; H, 5.4. $C_{22}H_{16}O_3$ requires C, 80.5; H, 4.9%); UV: 232 (4.51), 277 (4.05) and 330 (3.58); IR: 3400 (br), 1620 and 1595; 90 MHz PMR: 4.20 (*s*, 2H, $-CH_2Ph$), 6.57 (*d*, $J=9.5$ Hz, 1H, C_6-H), 7.00-7.38 (*bm*, 10H, $2\times-C_6H_5$), 8.07 (*d*, $J=9.5$ Hz, 1H, C_5-H), and 8.12 (*s*, 1H, C_2-H). Its acetate crystallized from methanol as colourless crystals, m.p. 118-20°; R_f 0.54 (solvent-C) (Found: C, 77.9; H, 4.5. $C_{24}H_{18}O_4$ requires C, 77.8; H, 4.9%); UV: 240 (4.5), 300 (4.0) and 390 (3.1); IR: 1755, 1615 and 1600; 90 MHz, PMR: 2.10 (*s*, 3H, $-OCOCH_3$), 4.10 (*s*, 2H, $-CH_2Ph$), 6.90 (*d*, $J=9.5$ Hz, 1H, C_6-H), 7.18-7.40 (*bm*, 10H, $2\times-C_6H_5$), 8.00 (*s*, 1H, C_2-H), and 8.20 (*d*, $J=9.5$ Hz, 1H, C_5-H).

6-*C-Benzyl-7-hydroxyisoflavone* (**5b**): Cream-coloured needles from ethyl acetate-pet. ether, m.p.

179-80°; R_f 0.45 (solvent-D) (Found: C, 80.0; H, 5.3. $C_{22}H_{16}O_3$ requires C, 80.5; H, 4.8%); UV: 234 (4.6), 302 (4.0) and 410 (3.1); IR: 3400 (br), 1625 and 1575; 90 MHz PMR: 4.02 (*s*, 2H, $-CH_2Ph$), 6.90-7.21 (*m*, 6H, $-C_6H_5$ and C_8-H), 7.35 (*s*, 5H, $-C_6H_5$ of ring-B), 7.91 (*s*, 1H, C_5-H), and 8.00 (*s*, 1H, C_2-H). Its acetate crystallized from hot petrol as colourless crystals, m.p. 137-38°; R_f 0.48 (solvent-C) (Found: C, 78.3; H, 5.1. $C_{24}H_{18}O_4$ requires C, 77.8; H, 4.9%); IR: 1750, 1615 and 1600; 200 MHz PMR: 2.00 (*s*, 3H, $-OCOCH_3$), 4.03 (*s*, 2H, $1\times -CH_2Ph$), 7.20-7.58 (*bm*, 11H, $2\times -C_6H_5$ and C_8-H), 8.00 (*s*, 1H, C_5-H), and 8.20 (*s*, 1H, C_2-H).

6,8-*Di-C-benzyl-7-hydroxyisoflavone* (**5c**): Yellow solid (20 mg) from benzene, m.p. 143-44°; R_f 0.67 (solvent-D) (Found: C, 83.0; H, 5.7. $C_{29}H_{22}O_3$ requires C, 83.2; H, 5.3%); UV: 266 (4.0), 302 (3.98), and 416 (3.81); IR: 1680, 1600 and 1520; 90 MHz PMR: 4.05, 4.23 (*s*, 2H each, $2\times -CH_2Ph$), 7.20-7.48 (*bm*, 15H, $3\times -C_6H_5$), 7.91 (*s*, 1H, C_6-H) and 8.04 (*s*, 1H, C_2-H). Its acetate crystallized from chloroform as light yellow needles, m.p. 88-90°; R_f 0.62 (solvent-B) (Found: C, 80.4; H, 5.7. $C_{31}H_{24}O_4$ requires C, 80.9; H, 5.3%); UV: 268 (4.5), 311 (4.18); IR: 1760, 1610 and 1600; 90 MHz PMR: 2.10 (*s*, 3H, $-OCOCH_3$), 3.84, 4.05 (2*s*, 2H each, $2\times -CH_2Ph$), 7.02-7.28 (*bm*, 15H, $3\times -C_6H_5$), 7.90 (*s*, 1H, C_5-H), and 8.05 (*s*, 1H, C_2-H).

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Aromatic Benzhydrylation: Part VIII—Synthesis of Benzhydrylated 2,3,4-Trihydroxydesoxybenzoin & Corresponding Isoflavones

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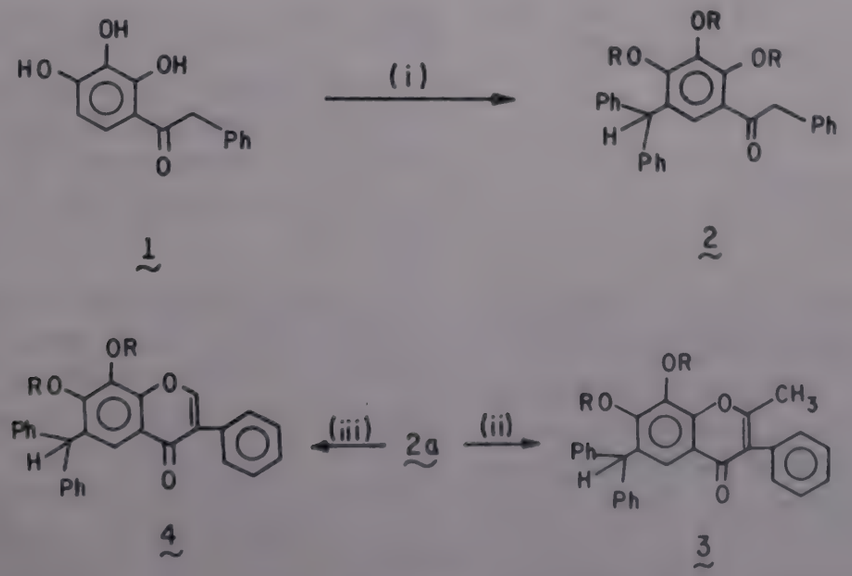
2,3,4-Trihydroxydesoxybenzoin (**1**) on reaction with diphenylcarbinol in the presence of $BF_3.Et_2O$ at room temperature affords only its 5-diphenylmethyl derivative (**2a**) which is converted into trimethyl derivative (**2b**), 6-diphenylmethyl-7,8-dihydroxyisoflavone (**4a**) and its 2-methyl derivative (**3a**). Their structural assignments are based on derivatisation and PMR data.

Aromatic benzhydrylation of 2,4-dihydroxydesoxybenzoin[1] and 2,4,6-trihydroxydesoxybenzoin[2] has been studied earlier. Now, we report nuclear benzhydrylation of 2,3,4-trihydroxydesoxybenzoin (**1**) with diphenylcarbinol in the presence of $BF_3.Et_2O$. The sole product was identified as 5-diphenylmethyl derivative (**2a**) on the basis of the formation of a trimethyl ether (**2b**) and PMR data. Both **2a** and **2b** showed only one singlet for an aromatic proton in their PMR spectra.

The benzhydrylated ketone **2a** on Perkin reaction with acetic anhydride and fused sodium acetate afforded 7,8-diacetoxy-2-methyl-6-diphenylmethylisoflavone (**3c**) which underwent smooth hydrolysis to yield 7,8-dihydroxy-2-methyl-6-diphenylmethylisoflavone (**3a**). Subsequent methylation yielded the dimethyl ether (**3b**). PMR spectra of all these three compounds showed 2-methyl group at δ2.34-2.48. Reaction of **2a** with DMF in the presence of CH_3SO_2Cl and $BF_3.Et_2O$ resulted in the formation of 7,8-dihydroxy-6-diphenylmethylisoflavone (**4a**) which formed a dimethyl ether (**4b**) and a diacetate (**4c**) derivatives. The PMR spectra of all these isoflavones showed a characteristic signal at δ7.56-7.95 due to C_2-H.

Unless stated otherwise, all m.ps are uncorrected; petrol used had the boiling range 60-80°; silica gel was used for column chromatography and solvent systems used for TLC were: (A) benzene, (B) benzene - ethyl acetate (19:1); R_f refers to TLC; UV spectra were recorded in MeOH on a Perkin-Elmer 554 spectrophotometer (λ_{max} in nm, log ε in parenthesis); IR spectra were measured using KBr on a Shimadzu model 535 spectrophotometer (ν_{max} in cm^{-1}); PMR spectra were taken in $CDCl_3$ on a Perkin-Elmer model



a R = H;
b R = CH_3;
c R = $COCH_3$;

REAGENTS USED :
(i) Ph_2CHOH, BF_3-Et_2O and
(ii) Ac_2O - NaOAc, 180°
(iii) DMF - CH_3SO_2Cl, BF_3-Et_2O, 0°

R-32 90 MHz using TMS as internal standard (chemical shifts in δ, ppm, and J values in Hz).

Benzhydrylation of **1**: *Formation of 2,3,4-trihydroxy-5-diphenylmethyldesoxybenzoin* (**2a**)

To a stirred solution of **1**[3] (4.68 g, 19.2 mmol) in dry dioxan (80 ml) was added a solution of diphenylcarbinol (3.5 g, 19.2 mmol) in dioxan (15 ml) followed by $BF_3.Et_2O$ (30 ml) in small lots. The resulting mixture was stirred at room temperature for 4 hr and diluted with ether (300 ml). The ethereal layer was washed with water, dried and solvent evaporated to dryness. The residue was column chromatographed and successively eluted with (i) petrol - benzene (3:7) and (ii) benzene to give **2a** and the unreacted **1** respectively. The product **2a** crystallized from ethyl acetate (3.2 g) m.p. 177-78°; R_f 0.34 (solvent-B) (Found: C, 78.9; H, 5.3; $C_{27}H_{22}O_4$ requires C, 79.0; H, 5.4%); UV: 296(4.6) and 262(4.44); IR: 3350, 1620, 1600, 1435, 1115 and 1050; PMR: 3.94(*s*, 2H, $-CH_2Ph$), 5.87[*s*, 1H, $-CH(Ph)_2$], 7.20(*s*, 1H, C_6-H), 7.36(*m*, 15H, $3 \times C_6H_5$), and 12.70(*s*, 1H, chelated OH).

It formed a trimethyl derivative (**2b**) with Me_2SO_4 and K_2CO_3 in acetone (10 hr) which crystallised from methanol as white needles, m.p. 113-14°; R_f 0.51(solvent-A) (Found: C, 79.5; H, 6.1, $C_{30}H_{28}O_4$ requires C, 79.6; H, 6.2%); UV: 258(4.42), 281(4.28) and 296(4.18); PMR: 3.42, 3.74 and 3.80(3*s*, 3*H* each, $3 \times -OCH_3$), 4.02(*s*, 2H, $-CH_2Ph$), 5.72[*s*, 1H, $-CH(Ph)_2$], 7.02(*s*, 1H, C_6-H), and 7.13(*m*, 15H, $3 \times C_6H_5$).

7,8-*Diacetoxy-6-diphenylmethyl-2-methylisoflavone* (**3c**) *and its derivatives* (**3a** *and* **3b**)

A solution of **2a** (500 mg) in acetic anhydride (10 ml) was heated with fused sodium acetate (500 mg) first at 135-40° for 1 hr and then at 180° for 6 hr. The resulting mixture was cooled, poured over crushed ice and the precipitated solid crystallised from methanol to give **3c** as light brown crystals (600 mg), m.p. 179-80°; R_f 0.35 (solvent-A) (Found: C, 76.0; H, 5.0. $C_{33}H_{26}O_6$ requires C, 76.4; H, 5.1%); UV: 262(4.1) and 298(4.39); PMR: 2.35(*s*, 3H, $-CH_3$), 2.05 and 2.26(2*s*, 3H each $2 \times OCOCH_3$), 5.67[*s*, 1H, $-CH(Ph)_2$], 7.10-7.35(*br m*, 15H, $3 \times C_6H_5$), and 7.68(*s*, 1H, C_5-H).

The above isoflavone (250 mg) on heating with 5% Na_2CO_3 (20 ml) at room temperature for 2 hr gave 6-diphenylmethyl-7,8-dihydroxy-2-methylisoflavone (**3a**) which crystallised from chloroform as light yellow plates, m.p. 223-24°; R_f: 0.45 (solvent-B) (Found: C, 80.1; H, 4.0. $C_{29}H_{22}O_4$ requires C, 80.2; H, 4.1%); UV: 265(4.82) and 300(4.62); IR: 3400, 1620, 1565, 1290 and 1060; PMR: 2.46(*s*, 3H, $-CH_3$), 5.93[*s*, 1H, $-CH(Ph)_2$], 7.05-7.29(*m*, 15H, $3 \times C_6H_5$), and 7.37(*s*, 1H, C_5-H).

Methylation of **3a** with Me_2SO_4(2.5 mol equiv.) in acetone containing K_2CO_3 for 4 hr gave 7,8-dimethoxy-2-methyl-6-diphenylmethylisoflavone (**3b**) which crystallised from benzene - petrol as colourless plates, m.p. 175-76°; R_f 0.40 (solvent-A) (Found: C, 80.4; H, 5.6. $C_{31}H_{26}O_4$ requires C, 80.5; H, 5.7%); UV: 260(4.22) and 298(4.6); IR: 1630, 1450, 1230, 1160 and 1030; PMR: 2.34(*s*, 3H, $-CH_3$), 3.58 and 4.0(2*s*, 3H each, $2 \times OCH_3$), 5.85[*s*, 1H, $-CH(Ph)_2$], 7.16-7.29(*m*, 15H, $3 \times C_6H_5$), and 7.52(*s*, 1H, C_5-H).

7,8-*Dihydroxy-6-diphenylmethylisoflavone* (**4a**) *and its derivatives* (**4b** *and* **4c**)

To a stirred and cooled solution of **2a** (500 mg) in DMF (10 ml) was added $BF_3.Et_2O$ (0.5 ml) dropwise during 0.5 hr. Temperature of the reaction mixture was raised to 60° and methanesulphonyl chloride (0.4 ml in 1 ml DMF) added to it in one lot. The reaction mixture was kept at room temperature for 1 hr and then heated on water-bath for 90 min, cooled and poured over crushed ice. The resultant solid crystallised from ethyl acetate when **4a** separated as yellow plates (0.5 g), m.p. 207-08°; R_f 0.43(solvent-B) (Found: C, 79.8; H, 5.0. $C_{28}H_{20}O_4$ requires C, 80.0; H, 4.8%); UV: 292(4.32), 260(4.44) and 240(4.52); IR: 3400, 1620, 1562, 1308, 1048 and 795; PMR: 5.76[*s*, 1H, $-CH(Ph)_2$], 6.83-7.11(*m*, 15H, $3 \times C_6H_5$), 7.26(*s*, 1H, C_5-H), and 7.56(*s*, 1H, C_2-H).

The above isoflavone (**4a**) was acetylated by Ac_2O-pyridine method (12 hr at room temperature) to give 7,8-diacetoxy-6-diphenylmethylisoflavone (**4c**) which crystallised from methanol as brown crystals, m.p. 191-2°; R_f 0.32(Found: C, 76.1; H, 4.6. $C_{32}H_{24}O_6$ requires C, 76.2; H, 4.8%); UV: 263(4.70), 298(4.26) and 310(4.22); PMR: 2.00 and 2.32(2*s*, 3H each, $2 \times OCOCH_3$), 5.61[*s*, 1H, $-CH(Ph)_2$], 7.10-7.40(*m*, 15H, $3 \times C_6H_5$), 7.74(*s*, 1H, C_5-H), and 7.91(*s*, 1H, C_2-H).

The isoflavone (**4a**) was methylated with Me_2SO_4 (2 mole equiv) as usual to form 7,8-dimethoxy-6-diphenylmethylisoflavone (**4b**). It crystallised from methanol as white needles, m.p. 179-80°; R_f

0.41(solvent-A) (Found: C, 80.6; H, 5.3. $C_{30}H_{24}O_4$ requires C, 80.3; H, 5.4%); UV: 263(4.57) and 296(4.15); PMR: 3.58 & 3.97(2*s*, 3H each, 2 × OCH_3), 5.87[*s*, 1H $-CH(Ph)_2$], 7.02-7.44(*m*, 15H, 3 × C_6H_5), 7.58(*s*, 1H, C_5-H), and 7.95(*s*, 1H, C_2-H).

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Synthesis of 9-Substituted 5-(*p*-Tolyl)-5,6,8,9,10,11-hexahydro-4*H*-isoquinolino[4,5-*g*]quinoline-4,6,8-triones (Condensed Naphthalimidopyridones) from 4-Amino-N-(*p*-tolyl)-naphthalimide

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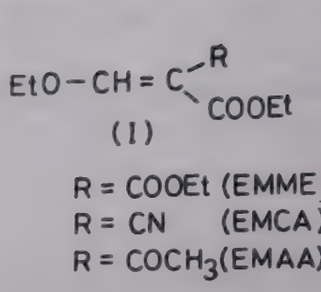
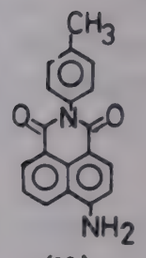
N-(*p*-Tolyl)naphthalimide-4-aminoacrylates (III) have been synthesised by the condensation of 4-amino-N-(*p*-tolyl) naphthalimide (II) with conjugated enol ethers (I). The resulting aminoacrylates undergo cyclisation by heating in dowtherm to yield 9-substituted 5-(*p*-tolyl)-5, 6, 8, 9, 10, 11-hexahydro-4*H*-isoquinolino [4,5-*g*] quinoline-4, 6, 8-triones (IV). The fluorescence characteristics of the aminoacrylates (in III) and the condensed naphthalimidopyridones (in IV) has been studied.



(I)

R = COOEt (EMME)
R = CN (EMCA)
R = $COCH_3$ (EMAA)



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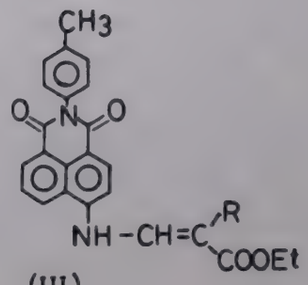
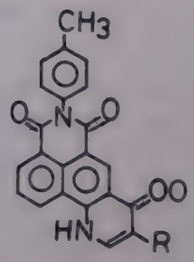


(III)



(IV)

4-Aminonaphthalimides and their derivatives are reported to be useful as fluorescent compounds[1-3]. 4-Amino-N-(*p*-tolyl) naphthalimide exhibits an intense yellow-green fluorescence in daylight in common organic solvents. Condensation of aromatic amino compounds with conjugated enol ethers to the corresponding aminoacrylates and subsequent cyclisation in dowtherm to the fused pyridone derivatives was followed in the synthesis of disperse dyes earlier in our laboratory[4,5].

In the present work it was envisaged to reduce the basicity of amino group in 4-amino-N-(*p*-tolyl) naphthalimide by extended conjugation with a view to investigating the fluorescence performance of the resulting aminoacrylates. As the incorporation of a heterocyclic moiety in the fluorescent compounds generally imparts better properties as compared to the corresponding open-chain compounds, it was therefore further envisaged to convert the aminoacrylates to the corresponding fused naphthalimidopyridones by cyclisation.

4-Amino-N-(*p*-tolyl) naphthalimide (II), prepared from acenaphthene by known procedures[6], was condensed with ethyl ethoxymethylenemalonic ester (EMME), ethyl ethoxymethylenecyanoacetic ester (EMCA) and ethyl ethoxymethyleneacetoacetic ester (EMAA) in an inert solvent (*p*-xylene) in the presence of a catalytic amount of piperidine to get ethyl β-N-(*p*-tolyl) naphthalimide-4-amino-α-(carbethoxy) acrylate (IIIa), ethyl β-N-(*p*-tolyl) naphthalimide-4-amino-α-(cyano) acrylate (IIIb) and ethyl β-N-(*p*-tolyl) naphthalimide-4-amino-α-(aceto) acrylate (IIIc) respectively in 55-65% yields. The above condensation when carried out in refluxing benzene gave III in low yields due to the formation of side products (as monitored by TLC) from the side reaction of amino group with the carbethoxy group in enol ethers. The aminoacrylates (IIIa-c) were refluxed in dowtherm for 18-24 hr, when the cyclisation took place with the elimination of ethanol resulting in the formation of fused naphthalimidopyridones, viz. 9-carbethoxy-5-(*p*-tolyl)-, 9-cyano-5-(*p*-tolyl)- and 9-acetyl-5-(*p*-tolyl)-5, 6, 8, 9, 10, 11-hexahydro-4*H*-isoquinolino [4,5-*g*] quinoline-4, 6, 8-triones (IVa-c) in 80-90% yields. The characterization data of the aminoacrylates (IIIa-c) and fused naphthalimidopyridones (IVa-c) are given in Table 1.

Among the enol ethers used in the condensation reactions of 4-amino-N-(*p*-tolyl) naphthalimide, EMME reacted the slowest and also gave the corresponding aminoacrylate in the lowest yield. Among the cyclisation reactions of IIIa-c, the cyclisation of aminoacrylate (IIIb) was the slowest.

The aminoacrylates (IIIa-c) exhibited an intense orange-blue fluorescence whereas fused naphthalimidopyridones (IVa-c) exhibited a weak red-green fluorescence in daylight in their DMF solutions. The fluorescence characteristics of these compounds were compared with those of a standard fluorescent compound, 7-diethylamino-4-methylcoumarin. The aminoacrylates (IIIa-c) exhibited a λ_{max} in the range 408-414 and a fluorescence emission band in the range 508-520 nm. Their intensity of fluorescence emission

Table 1—Characterization Data of N-(*p*-Tolyl)-naphthalimide-4-aminoacrylate (III) and 9-Substituted 5-(*p*-Tolyl)-5,6,8,9,10,11-hexahydro-4*H*-isoquinolino[4,5-*g*]quinoline-4,6,8-triones (IV)

Compd	R	Yield (%)	m.p.* °C	Mol. formula†
IIIa	$COOC_2H_5$	65.1	294-5	$C_{27}H_{24}N_2O_6$
IIIb	CN	59.7	287	$C_{25}H_{24}N_3O_4$
IIIc	$COCH_3$	55.0	268	$C_{26}H_{22}N_2O_5$
IVa	$COOC_2H_5$	89.8‡	>340	$C_{25}H_{18}N_2O_5$
IVb	CN	92.0‡	>340	$C_{23}H_{13}N_3O_3$
IVc	$COCH_3$	79.9‡	>340	$C_{24}H_{16}N_2O_4$

*Melting points are uncorrected.
†All compounds gave satisfactory elemental analyses.
‡Yields of IVa-c are based on IIIa-c.

was found comparable with that of the standard. The fused naphthalimidopyridones (IVa-c) exhibited a λ_{max} in the range 438-458 and the fluorescence emission band in the range 480-495 nm. They, however, showed poor fluorescence intensity.

The aminoacrylates (IIIa-c) and fused naphthalimidopyridones (IVa-c) were applied on polyester as disperse dyes. The dyeings obtained in the case of IIIa-c showed good exhaustion, excellent light and sublimation fastness and resulted in brilliant greenish-yellow shades on polyester. The fused naphthalimidopyridines (IVa-c), however, showed poor exhaustion with dull shades.

4-Amino-N-(*p*-tolyl) naphthalimide (II) was prepared from acenaphthene by a series of reactions following known procedures[6].

N-(p-Tolyl)naphthalimido-4-aminoacrylates (IIIa-c): General procedure

To a stirred mixture of 4-amino-N-(*p*-tolyl) naphthalimide (II) (3.02 g, 0.01 mol) and dry xylene (20 ml) was added a solution of the conjugated enol ether (0.011 mol of EMME, EMCA or EMAA) in dry xylene (5-10 ml) with stirring. Piperidine (1 or 2 drops) was then added to the reaction mixture and the contents were heated to reflux for 8-10 hr with TLC monitoring. The boiling reaction mixture was filtered, the filtrate concentrated and cooled to give a crystalline solid which recrystallised from xylene to give pure III in 55-65% yield (Table 1).

9-Substituted 5-(p-tolyl-5,6,8,9,10,11-hexahydro-4H-isoquinolino [4,5-g] quinoline-4,6,8-triones (IVa-c): General procedure

The aminoacrylate III (0.01 mol) was added to dowtherm (20-25 ml) and the mixture heated to boiling with stirring for 18-24 hr with TLC monitoring, cooled and pet. ether (30-40 ml) added to it. The separated solid was filtered, washed with pet. ether and crystallised from acetic acid to give IV in 80-92% yield (Table 1).

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Synthesis of Condensed Pyrimidines: Reactions of Heterocyclic Amines with Ethoxymethylene Malonate & Ethyl Benzoylacetate

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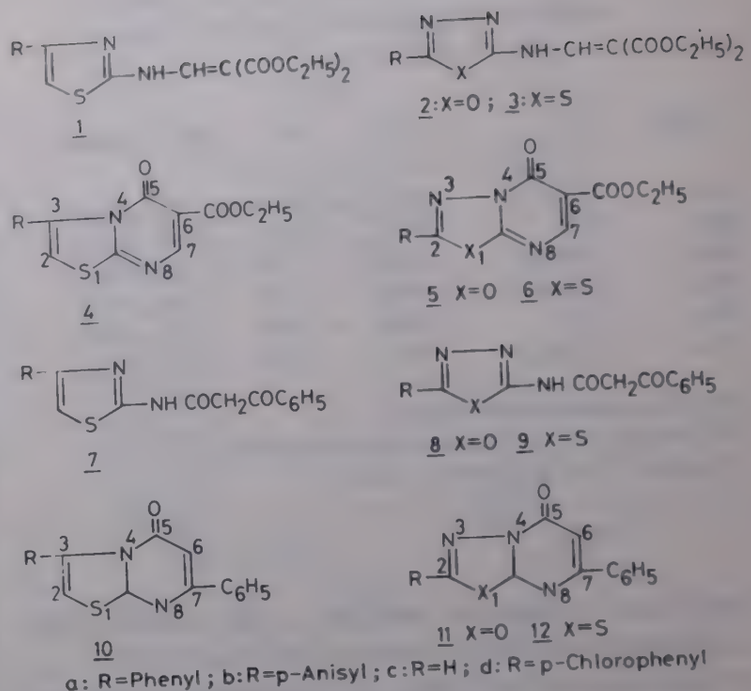
A few 3-aryl-6-carbethoxythiazolo[3,2-*a*]-(**4**) and 2-aryl-6-carbethoxy-1,3,4-oxa/thiadiazolo[3,2-*a*]-pyrimidin-5(*H*)-ones (**5,6**) have been synthesized by the reactions of aminothiazoles and amino-oxathiadiazoles respectively with diethyl ethoxymethylenemalonate. The reaction of these amines with ethyl benzoylacetate furnishes 7-phenylpyrimidin-5(*H*)-one derivatives (**10-12**). The structures of these compounds have been established by spectral data and isolation of the intermediates.



In our previous communication on the synthesis of purine based heterocycles[1], we reported the synthesis of several 5-carbethoxy-1,3,4-thiaoxadiazolo[3,2-*a*]- and 3-aryl-5-carbethoxythiazolo-[3,2-*a*]-pyrimidin-7(*H*)-ones by condensing the heterocyclic amines with diethyl acetylenedicarboxylate. We now report the synthesis of a new series of isomeric condensed pyrimidines by refluxing the same amines with diethyl ethoxymethylenemalonate in trichlorobenzene for 4-5 hr. These compounds were characterized as 6-carbethoxy derivatives (**4,5** and **6**; Table 1) by spectral studies and isolation of aminomethylenemalonate intermediates (**1, 2** and **3**). The $\nu C=O$ bands appearing in these compounds at 1675-1700 and 1730-1760 cm^{-1} corresponded to the C-5 carbonyl and ester carbonyl at C-6 respectively and were in good agreement with our earlier findings[1] on pyrimidin-5-one derivatives and also with those of Daneshtalab *et al.*[2]

A new series of condensed pyrimidines were also synthesised by reacting the amines with ethyl benzoylacetate. The reaction in toluene containing a catalytic amount of p-toluenesulphonic acid gave the uncyclised products (**7-9**) which underwent cyclization in conc. H_2SO_4 through an imino intermediate to give **10-12**. This type of rearrangement has been observed by Seide[3] with pyridine system. The possibility for the formation of isomeric 5-phenyl derivatives was ruled out as they have been prepared by us[1] using ethyl phenylpropiolate.

Melting points are uncorrected. IR spectra in KBr were taken on a Perkin-Elmer model 293 spectrophotometer (ν_{max} in cm^{-1}). The heterocyclic amines were prepared according to the procedure available in literature.

Table 1—Characterization Data of Condensed Pyrimidines (4-6 and 10-12)

Compd	m.p. °C	Mol. formula	Found (%) (calc.)	
			S	N
4b	222	$C_{16}H_{14}N_2SO_4$	9.5 (9.6	8.2 8.4)
4d	254	$C_{15}H_{11}N_2SO_3Cl$	9.4 (9.5	— —)
5a	247	$C_{14}H_{11}N_3O_4$	— (	14.8 14.7)
5b	>250	$C_{15}H_{13}N_3O_6$	— (	13.2 13.3)
6a	>250	$C_{14}H_{11}N_3SO_3$	10.5 (10.6	13.8 14.0)
6b	>250	$C_{15}H_{13}N_3O_4S$	9.5 (9.7	12.5 12.7)
6c	>250	$C_8H_7N_3SO_3$	14.1 (14.2	18.3 18.6)
10b	244	$C_{19}H_{14}N_2SO_2$	9.3 (9.6	8.1 8.4)
11a	>250	$C_{17}H_{11}N_3O_2$	— (—	14.4 14.5)
12c	232	$C_{11}H_7N_3OS$	13.8 (13.9	18.2 18.3)

3-Phenyl-6-carboethoxythiazolo[3,2-*a*]-*pyrimidin-5*(*H*)*-one* (**4a**)

A mixture of 2-amino-4-phenylthiazole (0.42 g) and diethyl ethoxymethylenemalonate (0.7 g) in 1,2,4-trichlorobenzene was refluxed for 4-5 hr and cooled.

The separated buff coloured crystals were recrystallised from DMF, m.p. 166°, yield 100 mg (18%) (Found: S, 10.4 $C_{15}H_{12}N_2SO_3$ requires S, 10.7%); IR: 1745 (C-6 ester carbonyl), 1690 (C-5 isolated carbonyl).

Diethyl 4-phenylthiazol-2-ylaminomethylenemalonate (**1a**)

A mixture of 2-amino-4-phenylthiazole (1.7 g) and diethyl ethoxymethylenemalonate (2.1 g) was heated at 110-120° for 45 min, cooled, diluted with benzene (5 ml) and excess of pet. ether (b.p. 60-80°C) added to it. The separated yellow solid was recrystallised from benzene to get **1a**, m.p. 96° (Found: S, 9.9. $C_{17}H_{18}N_2SO_4$ requires S, 10.3%); IR: 3300 (−NH), 1690 and 1660 (two carbonyls).

Following compounds were also prepared in a similar way.

Diethyl 4-p-anisylthiazol-2-ylaminomethylenemalonate (**1b**): m.p. 115°.

Diethyl 4-(*p*-chlorophenyl)thiazolyl-2-aminomethylenemalonate (**1d**): m.p. 136°.

Diethyl 5-phenyloxadiazol-2-ylaminomethylenemalonate (**2a**): m.p. 139°.

Diethyl 5-*p*-anisyloxadiazol-2-ylaminomethylenemalonate (**2b**): m.p. 172°.

Diethyl 5-phenylthiadiazol-2-ylaminomethylenemalonate (**3a**): m.p. 200°.

Diethyl 5-p-anisylthiadiazol-2-ylaminomethylenemalonate (**3b**): m.p. 213°.

Diethyl 1,3,4-thiadiazol-2-ylaminomethylenemalonate (**3c**): m.p. 190°.

Cyclisation of **1a** *to* **4a** *using PPA*

The aminomethylene intermediate **1a** (0.5 g) in PPA (5 g) was heated for 4 hr at 110°. The cooled reaction mixture was neutralised with dil. ammonia. After cooling in ice for several hours, a colourless solid separated out which was recrystallised from ethanol to give **4a**, m.p. and m.m.p. 166°, yield 100 mg (20%).

N-(4-phenylthiazol-2-yl)benzoylacetamide (**7a**)

A mixture of 2-amino-4-phenylthiazole (0.4 g), ethyl benzoylacetate (0.6 g) and *p*-toluenesulphonic acid (0.1 g) in dry toluene was refluxed for 40 hr, cooled and the crystalline solid filtered, m.p. 180°, yield 0.3 g (50%) (Found: S, 9.5. $C_{18}H_{14}N_2SO_2$ requires S, 9.9%); IR: 3400 (−NH), 1670 and 1695 (two carbonyl groups).

Following compounds were also prepared in a similar way.

N-(4-*p*-Anisylthiazol-2-yl)benzoylacetamide (**7b**): m.p. 185°.

N-(4-*p*-Chlorophenylthiazol-2-yl)benzoylacetamide (**7d**): m.p. 196°.

N-(5-Phenyloxadiazol-2-yl)benzoylacetamide (**8a**): m.p. 210°.

N-(5-*p*-Anisyloxadiazol-2-yl)benzoylacetamide (**8b**): m.p. 226°.

N-(5-Phenylthiadiazol-2-yl)benzoylacetamide (**9a**): m.p. 165°.

N-(5-*p*-Anisylthiadiazol-2-yl)benzoylacetamide (**9b**): m.p. 182°.

N-(1,3,4-thiadiazol-2-yl)benzoylacetamide (**9c**): m.p. 170°.

Cyclisation of **7a** *to* **10a** *using acetic anhydride*

A solution of **7a** (0.3 g) in acetic anhydride (15 ml) containing a little pyridine (1 ml) was refluxed for 4 hr, cooled and poured into ice. The solid obtained was filtered and recrystallised from ethanol to give **10a**, m.p. 203°, yield 150 mg (55%) (Found: S, 10.3. $C_{18}H_{10}N_2SO$ requires S, 10.5%); IR: 1700 (C=O).

The same compound was also obtained when the cyclisation was carried out using H_2SO_4.

The characterization data of other compounds (**10b**, **11a**, **12c**) are given in Table 1.

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An Improved Synthesis of α-*n*-Amylcinnamaldehyde Based on Liquid Phase Transfer

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α-*n*-Amylcinnamaldehyde is synthesised by the condensation of benzaldehyde with *n*-heptanal using anhydrous potassium carbonate and benzyltriethylammonium chloride as a phase transfer catalyst in dichloromethane. This method is superior to other methods with regard to yield which is ~80%. Two other substituted α-*n*-amylcinnamaldehydes have also been obtained by a similar procedure.

The synthesis of α-*n*-amylcinnamaldehyde, an ingredient used in perfumery compositions, involves the condensation of benzaldehyde with *n*-heptanal using sodium hydroxide[1] or phosphorous oxychloride[2] as the condensing agent. However, there are various side products, the most important being the self-condensation product of *n*-heptanal, namely 2-*n*-amyl-Δ^2-*n*-nonenyl aldehyde[3].

The convenient approach for the target compound now developed involves aldol condensation of benzaldehyde with heptanal, using molar proportion of anhydrous potassium carbonate and phase transfer catalyst namely, benzyltriethylammonium chloride (BTEAC). Experimental conditions have been designed in such a way as to give minimum amount of the self condensation product of heptanal.

The use of mild base in the two-phase system considerably prevents resinification of the starting aldehyde. This method affords α-*n*-amylcinnamaldehyde in 80% yield. The use of cetyltrimethylammonium chloride offers no special advantage over BTEAC.

Using a similar reaction condition anisaldehyde and veratraldehyde have been condensed with *n*-heptanal to afford respectively 4-methoxy-α-*n*-amylcinnamaldehyde (b.p. 150-52°/0.5 mm, reported 145°/0.3 mm) and 3,4-dimethoxy-α-,*n*-amylcinnamaldehyde[5] (b.p. 164°/0.6 mm, reported[5] 165°/0.6 mm) in 75% and 70% yields respectively.

In a control experiment, using same experimental conditions but without using any catalyst, the yield of α-*n*-amylcinnamaldehyde was 60%, thus showing that the catalyst has some definite role to play. It is also observed that by using lower amounts of catalyst than 1 molar equivalent the yield is decreased.

In an actual experiment, *n*-heptanal (2.28 g, 0.02 mol) was added dropwise during 30 min to a uniformly stirred solution of benzaldehyde (2.12 g, 0.02 mol) in dichloromethane (10 ml) to which anhydrous potassium carbonate (2.76 g) and BTEAC (2.5 g) have been added. Stirring was continued for 3 hr, the mixture diluted with water, the organic layer separated and the aqueous layer extracted with dichloromethane. The combined organic extract was evaporated after drying (Na_2SO_4), and the residual oil further distilled under reduced pressure to afford α-*n*-amylcinnamaldehyde as a pale yellow oil (3.21 g), b.p. 140°/5 mm (lit.[4] 145°/0.5 mm), yield 80% (Found: C, 83.3, H, 8.8. Calc. for $C_{14}H_{18}O$: C, 83.1; H, 8.9%), semicarbazone, m.p. 117° (reported 117.5-18°).

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Perbenzoic Acid Oxidation of 3β-Acetoxycholest-5-en-7-one Oxime

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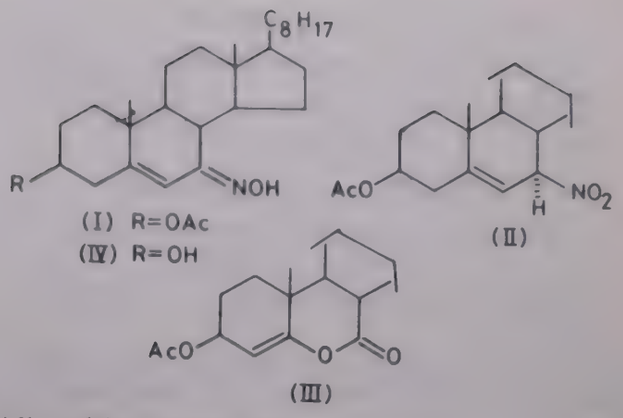
Perbenzoic acid oxidation of 3β-acetoxycholest-5-en-7-one oxime (I) furnishes 3β-acetoxy-7β-nitrocholest-5-ene (II), 3β-acetoxy-6-oxa-cholest-4-en-7-one (III) and 3β-hydroxycholest-5-en-7-one oxime (IV).

A number of methods are available for the synthesis of nitrosteroids[1-5], but some of these are rather drastic. This note describes a simple method using perbenzoic acid as an oxidant for the conversion of steroidal oximes into the nitro derivatives.

Thus, 3β-acetoxycholest-5-en-7-one oxime (I)[8] on perbenzoic acid oxidation, afforded the nitrosteroid (II), oxa-steroid (III) and hydroxy-oxime (IV). Compound (II) analysed for $C_{29}H_{47}NO_4$ and exhibited in its IR spectrum in nujol bands at 1730, 1273 (CH_3COO), 1630 (C=C) and 1535 cm^{-1} (C−NO_2). The PMR spectrum of II displayed a one-proton multiplet at δ 4.9 ($W_{\frac{1}{2}}$=16 Hz)[6] assignable to $C_3-\beta H$, a singlet at 6.5 for C-6 vinylic proton and a sharp singlet at 2.01 for acetate moiety at C-3. A broad singlet at δ 3.3 for $C_7-\alpha H$ confirms the presence of nitro group at C-7 as β-oriented. The above data led to the structure as 3β-acetoxy-7β-nitrocholest-5-ene for II.

Compound (III), $C_{28}H_{44}O_4$, exhibited in its IR spectrum in nujol bands at 1810 (CO of a six-membered lactone)[7], 1745 (CH_3COO) and 1630 cm^{-1} (C=C). In the PMR spectrum a multiplet at δ 4.06 for $C_3-\alpha H$ (axial, $W_{\frac{1}{2}}$=17 Hz) and a singlet at 2.0 for acetate moiety were seen. The C-4 vinylic proton appeared at δ 6.4 as a broad singlet. The above data connirmed the III as 3β-acetoxy-6-oxa-cholest-4-en-7-one.

Compound (IV), which analysed for $C_{27}H_{45}NO_2$, exhibited in its IR spectrum bands at 3420 (−OH), 3280 (=NOH), 1630 (C=C) and 1460 cm^{-1} (C=N−). Its PMR spectrum exhibited a sinolet at δ 6.6 ascribable to C-6 vinylic proton and two broad peaks at 8.3 and 9.2 (exchangeable with D_2O) assignable to =NO*H* and O*H* respectively. The $C_3-\alpha H$ appeared at δ 3.8 ($W_{\frac{1}{2}}$=18 Hz). On the basis of above data IV was assigned the structure as 3β-hydroxycholest-5-en-7-one oxime.



All melting points were determined on a Kofler's block and are uncorrected. Petroleum ether refers to fraction, b.p. 60-80°.

Perbenzoic acid oxidation of 3β-acetoxycholest-5-en-7-one oxime (I)

3β-Acetoxycholest-5-en-7-one oxime[8] (I, 2 g) in chloroform (30 ml) was treated with a solution of perbenzoic acid (1.1 mol) in chloroform at 0°C, left at room temperature for 48 hr and worked-up in chloroform. The chloroform solution was washed with water, sodium aq thiosulphate (5%) and water and dried (Na_2SO_4). Removal of the solvent under reduced pressure provided a residue (1.8 g) which was chromatographed over silica gel (40 g). The column was successively eluted with 20:1, 10:1 and 1:1 light petrol-ether to give three fractions respectively. Fraction-1 gave II as an oil which crystallized from methanol (750 mg), m.p. 148° (Found: C, 73.5; H, 9.9; N, 2.9. $C_{29}H_{47}NO_4$ requires C, 73.6; H, 9.9; N, 3.0%).

Fraction-2 afforded III as a white solid, which recrystallized from light petroleum ether as needles (500 mg), m.p. 209° (Found: C, 75.6; H, 9.9. $C_{28}H_{44}O_4$ requires C, 75.7; H, 9.9%).

Fraction-3 gave IV, which recrystallized from light petroleum ether as a white solid (380 mg), m.p. 218° (Found: C, 78.8; H, 10.8; N, 3.4. $C_{27}H_{45}NO_2$ requires C, 78.1; H, 10.8; N, 3.4%).

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Sodium Hydrogen Telluride—A New Convenient Reagent for Deblocking Allyl Carboxylates & Allyl Phenyl Ethers

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Sodium hydrogen telluride is found to be a mild and effective reagent for cleaving allyl carboxylates as well as allyl phenyl ethers.

During degradation as well as synthesis of large and complex organic molecules a need often arises, at some stage or other of the total process, to protect carboxyl, phenolic and other functional groups present. The protective groups employed for various functionalities are well documented in the literature[1]. For a carboxyl function, the usefulness of cinnamyl as a protective group has recently been demonstrated by Corey and Tius[2]. The technique employed for deblocking[2] the cinnamyl ester involved treatment of the ester with mercuric acetate in methanol solution, followed by demercuriocarboxylation of the resulting methoxymercurated product with aqueous potassium thiocyanate. The possibility that ally group might be functionally equivalent to cinnamyl in serving as a protective group for carboxylic acids appears attractive, but the mercuration-demercuration sequence, as reported by Ho[3], is not applicable to allyl carboxylates, as the mercuri-group would be attached to the terminal carbon atom of the allyl moiety during solvato mercuration. He however demonstrated the utility of lithium dimethylcuprate[3] as a reagent for the selective deblocking of allyl esters.

In continuation of our work on sodium hydrogen telluride which has proved to be a versatile reagent for the reduction[4] of carbon-carbon double bonds, and for the deacylation[5] of phenyl acetates and benzoates, we wish to report now on the utility of sodium hydrogen telluride as a mild and efficient reagent for deblocking allyl carboxylates under essentially neutral conditions. When allyl benzoate (**1a**) was refluxed (2 hr) with sodium hydrogen telluride in ethanol, it readily underwent deallylation to give benzoic acid (**1b**). A similar behaviour was observed with the esters (**2a**) and (**3a**) giving the acids (**2b**) and (**3b**), respectively (Table 1).

Interestingly when allyl ether of phenol (**4a**) was heated (2 hr) with the same reagent it readily underwent deallylation to give phenol (**4b**). The allyl ethers (**5a**) and (**6a**) likewise underwent similar deallylation to the hydroxy compounds (**5b**) and (**6b**), respectively (Table 1).

Table 1—Deallylation Using Sodium Hydrogen Telluride

Substrate	Product	Yield (%)
Allyl benzoate (**1a**)	Benzoic acid (**1b**)	95
Allyl anisate (**2a**)	Anisic acid (**2b**)	95
Allyl crotonate (**3a**)	Crotonic acid (**3b**)	95
Allyl phenyl ether (**4a**)	Phenol (**4b**)	95
4-allyloxycourmarin (**5a**)	4-Hydroxycoumarin (**5b**)	99
4-allyloxy-2-quinolone (**6a**)	2,4-Dihydroxyquinoline (**6b**)	85

General procedure

To a solution of sodium hydrogen telluride [prepared *in situ*[6] from tellurium powder (1.30 g) and sodium borohydride (0.90 g) in ethanol (20 ml)], buffered with deoxygenated acetic acid (1.2 ml in 5 ml ethanol) was added the allyl carboxylate/allyl phenyl ether (0.005 mol). The mixture was refluxed, under a cover of N_2 for 2 hr, after which the solution was filtered, the filtrate evaporated, and the residue dissolved in water. The aqueous layer was made slightly acidic with a few drops dil. HCl. The aqueous layer was then extracted with $CHCl_3$ [except in cases of (**5**) and (**6**) wherein the phenols crystallised from the aqueous solutions on standing], dried and evaporated. The residue was purified by recrystallisation or distillation as the case may be.

The products (Table 1) were fully characterised by direct comparison (co-TLC, co-IR, m.p./b.p.) with authentic samples.

We thank the CSIR, New Delhi for the award of a senior research fellowship to one of us (NS) and Mr M Palaniswamy for IR spectra.

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Fragmentation of N-Aryl- & N-Aralkyl-N′,N″-dicarbomethoxyguanidines with Thiophosgene†

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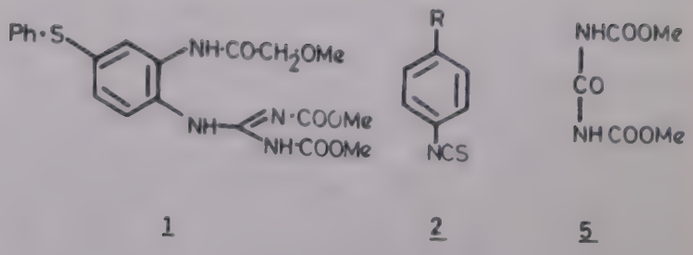
N-Aryl- and N-aralkyl-N′,N″-dicarbomethoxyguanidines (**3**) on treatment with thiophosgene undergo fragmentation to yield N,N′-dicarbomethoxyurea (**5**) and the isothiocyanates.

N-Aryl-N′,N″-dicarbomethyoxyguanidines exemplified by febantel (**1**)[1] and aryl isothiocyanates exemplified by bitoscanate (**2a**)[2] and amoscanate (**2b**)[3] represent classes of potent anthelmintics. In the course of our efforts to prepare compounds having both the groups, we find that the dicarbomethoxyguanidines (**3**) on treatment with thiophosgene undergo a novel fragmentation leading to the corresponding isothiocyanates and N,N′-dicarbomethoxyureas (**5**).

Compounds (**3a-3k**) on treatment with thiophosgene yield **5**, the yields being 50-60% in the case of the aryl derivatives (**3a-3i**) and 15-20% in the case of the aralkyl derivative (**3j, k**). The aryl isothiocyanates formed in the reaction of **3a-3g** were characterised as the known morpholine adducts **4a-4g** respectively. From **3h** and **3i**, the isothiocyanates were isolated as such and identified by direct comparison with authentic samples as *p*-nitrophenyl isothiocyanate and 1,4-phenylene bisisothiocyanate (**2a**) respectively. In the case of **3j, k**, the isothiocyanates formed in low yields apparently decomposed in the reaction and attempts to isolate them as such or as the morpholine adducts did not succeed.

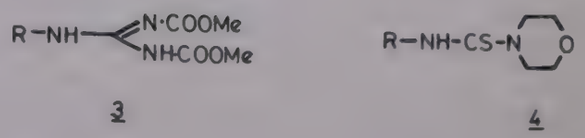
The fragmentation of **3** with thiophosgene may involve either of the two following paths (Scheme 1). Both lead to the isothiocyanate and dicarbomethoxycarbodiimide (**6**), the latter yielding **5** by hydration.

The reported reaction of the amidine (**7**)[4] with thiophosgene bears a close analogy to the above fragmentation.



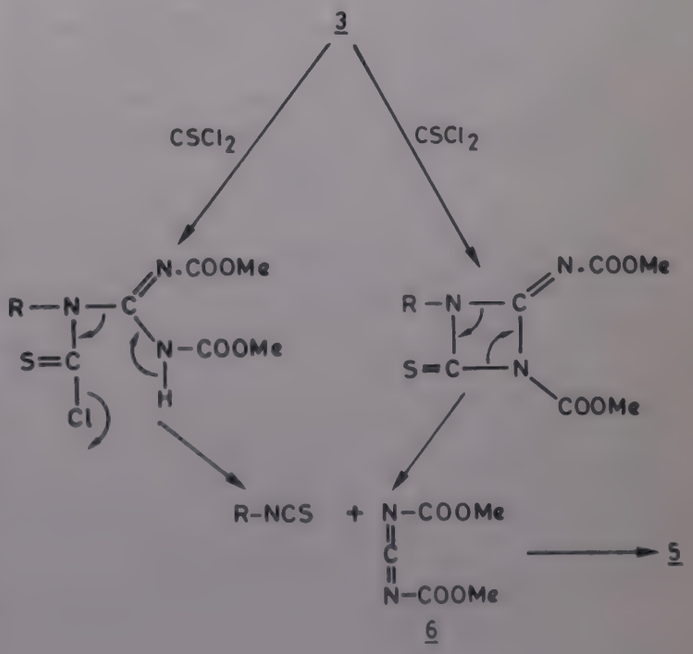
1 2 5

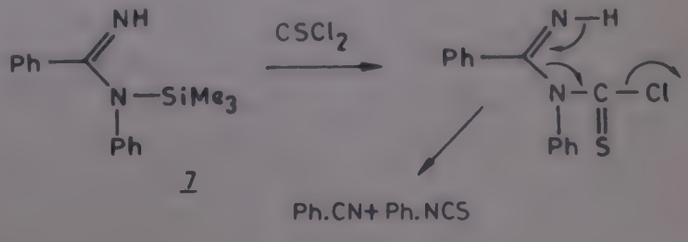
a : R = NCS
b : R = -NH-C6H4-NO2



3 4

R		R	
a	phenyl	g	1-naphthyl
b	p-chlorophenyl	h	p-nitrophenyl
c	m-chlorophenyl	i	p-aminophenyl
d	p-bromophenyl	j	benzyl
e	p-tolyl	k	2-phenylethyl
f	p-methoxyphenyl		





Experimental Procedure

Melting points are uncorrected. Satisfactory microanalyses for C, H and N (±0.4%) were obtained for all new compounds reported.

†Communication No. 791 from HINDUSTAN CIBA-GEIGY Research Centre.

General procedure for preparation of **3**.

A solution of amine (0.05 mol) in methanol (60 ml) was refluxed with N,N'-dicarbomethoxy-S-methyl-pseudothiourea (0.06 mol) and *p*-toluenesulphonic acid (0.1 g) for 3 hr and the product filtered to yield **3** (yield 70-80%). Thus were obtained: **3a**[5], $C_{11}H_{13}N_3O_4$, m.p. 81°; **3b**[6], $C_{11}H_{12}ClN_3O_4$, m.p. 121° ; **3c**[7], $C_{11}H_{12}ClN_3O_4$, m.p. 129°; **3d**, $C_{11}H_{12}BrN_3O_4$, m.p. 113°; **3e**, $C_{12}H_{15}N_3O_4$, m.p. 131°; **3f**[8], $C_{12}H_{15}N_3O_5$, m.p. 96°; **3g**, $C_{15}H_{15}N_3O_4$, m.p. 155°; **3h**, $C_{11}H_{12}N_4O_6$, m.p. 160°; **3i**, $C_{11}H_{14}N_4O_4$, m.p. 142°; **3j**[5,8], $C_{12}H_{15}N_3O_4$, m.p. 88° and **3k**, $C_{13}H_{17}N_3O_4$, m.p. 116°.

General procedure for the thiophosgene reaction with **3**

A solution of **3** (2 g) in dioxane (20 ml) was stirred at 5° and treated with thiophosgene (1 ml) in dioxane (6 ml) and water (2 ml). The solution was stirred overnight at room temperature, diluted with water and extracted with methylene chloride-hexane to yield **5**, m.p. 155-57° (lit.[9], m.p. 154-55°); IR (nujol): 3215, 3160, 1805, 1735 cm^{-1}; MS (relative intensity in parentheses): *m/z* 176 (M^+; 70), 145 (100), 118 (40) (Found: C, 34.2; H, 5.0; N, 15.5. Calc. for $C_5H_8N_2O_5$: C, 34.1; H, 4.6; N, 15.9%).

The mother liquors from **5** on evaporation gave a residue showing ν_{max} CH_2Cl_2 at 2050 cm^{-1} (NCS). From **3h** and **3i**, the isothiocyanates, obtained as solid products were identified by direct comparison (m.m.p., IR) with authentic samples as *p*-nitrophenyl isothiocyanate, m.p. 110°, and 1,4-phenylene-bisisothiocyanate (**2a**), m.p. 125°, respectively. In the case of the other aryl isothiocyantes, the crude product in ether (10 ml) was treated with morpholine (0.8 g) and left overnight at room temperature. The products (**4a-4g**) were crystallised from methylene chloride-hexane and identified by direct comparison (m.m.p., IR spectra) with authentic samples. Thus were obtained: **4a**[10], $C_{11}H_{14}N_2OS$, m.p. 132°; **4b**[11], $C_{11}H_{13}ClN_2OS$, m.p. 170°; **4c**[10], $C_{11}H_{13}ClN_2OS$, m.p. 162°; **4d**[11], $C_{11}H_{13}BrN_2OS$, m.p. 180°; **4e**[11], $C_{12}H_{16}N_2OS$, m.p. 148°; **4f**[11], $C_{12}H_{16}N_2O_2S$, m.p. 158° and **4g**[11], $C_{15}H_{16}N_2OS$, m.p. 162°, respectively from **3a-3g**.

We thank Dr S Rajappa for his interest in the work.

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Relative Binding Affinity & Antiimplantation Activity of 2,6β-Diethyl-3-(2-methyl-4-hydroxyphenyl)-bicyclo[4.3.0]non-2-en-7β-ol†‡

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Synthesis, relative binding affinities (RBA) to estradiol-17β receptors and antiimplantation activities of a few seco-derivatives of β-homoestradiol are reported. Two of the compounds synthesised (3 and 4) are found to be the most active and prevent implantation in rats at 2 mg/kg dose.

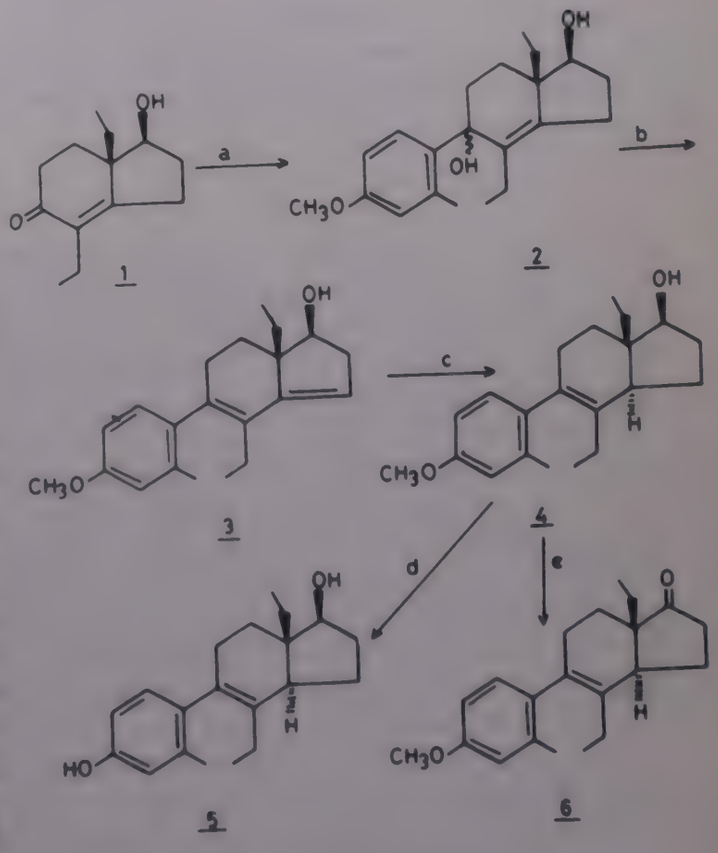
A systematic study of secoestradiol derivatives has been in progress in this laboratory with a view to developing antifertility agents with minimal hormonal activity. It was observed that some B-secoestradiol derivatives[1-4] showed significant antifertility activity. As an extension of this work we report herein the synthesis of 2,6β-diethyl-3-(2-methyl-4-hydroxyphenyl)-bicyclo[4.3.0]non-2-en-7β-ol (**5**) and some related compounds, their relative binding affinities (RBA) to estradiol-17β receptors and antifertility activities.

Condensation of 2,6β-diethyl-7β-hydroxybicyclo-[4.3.0]non-1-en-3-one (**1**)[2] with 2-methyl-4-methoxyphenyllithium (prepared[2] from equimolar amounts of 3-methyl-4-bromoanisole and butyllithium) gave 2,6β-diethyl-3-hydroxy-3-(2-methyl-4-methoxyphenyl)-bicyclo[4.3.0]non-1-en-7β-ol(**2**) as a colourless solid which crystallised from benzene-hexane, yield 83%; m.p. 123-24°; PMR: 0.9 (*t*, 6H, 2-CH_2CH_3 and 6-CH_2CH_3), 2.43 (*s*, 3H, $ArCH_3$), 3.65 (*s*, 4H, OCH_3 and at base 7α-H), 6.3-6.9 (*m*, 3H, ArH). Unlike the corresponding 2-desmethyl compound[1,2], **2** was quite stable but underwent dehydration in refluxing benzene in the presence of *p*-toluenesulfonic acid for 2 hr to give 2,6β-diethyl-3-(2-methyl-4-methoxyphenyl)bicyclo-[4.3.0]nona-2,9-dien-7β-ol (**3**) as an oil; yield 84%; PMR: 0.88 (*m*, 6H, 2-CH_2CH_3, 6-CH_2CH_3), 3.68 (*s*, 3H, OCH_3), 4.08 (*t*, 1H, 7α-H, J = 9 Hz), 5.43 (distorted *t*, 1H, =CH), 2.45 (*s*, 3H, $ArCH_3$), 6.45-6.9 (*m*, 3H, ArH).

Catalytic hydrogenation of **3** in ethanol over 10% Pd/C, till 1 mol of hydrogen was absorbed, furnished 2,6β-diethyl-3-(2-methyl-4-methoxyphenyl)bicyclo-[4.3.0]non-2-en-7β-ol (**4**) as an oil; yield 92%; PMR: 0.73 (*t*, 3H, 2-CH_2CH_3), 1.00 (*t*, 3H, 6-CH_2-CH_3), 2.1 (*s*, 3H, $ArCH_3$), 3.63 (*s*, 4H, OCH_3 and at base 7α − *H*), 6.47-6.9 (*m*, 3H, ArH); mass: *m/z* 314(M^+). The *trans*-stereochemistry of **4** was decided on the basis of upfield shift of angular methyl group in PMR as described earlier[1-3].

All attempts to reduce the 2,3-double bond both in **3** or **4** either by catalytic hydrogenation under different conditions or by Birch reduction were unsuccessful. Even hydrogenolysis of **2** to remove the benzylic hydroxy group met with failure. Use of hydride shift reagent, triethylsilane along with trifluoroacetic acid[5] was also unsuccessful.

Demethylation of **4** by heating it with hydrazine hydrate, KOH and diethylene glycol at 225° under nitrogen for 2 hr gave 2,6β-diethyl-3-(2-methyl-4-hydroxyphenyl)bicyclo[4.3.0]non-2-en-7β-ol (**5**) as a colourless solid; yield 56%; m.p. 130°; PMR: 2.5 (*s*, 3H,



a 3-Methyl-4-bromoanisole /n-BuLi
b Benzene, PTSA
c 10% Pd/C, H_2 (1 mol)
d KOH, diethylene glycol, hydrazine hydrate
e Jone's reagent

Scheme-1

†CDRI Communication No. 3736.
‡Part 48 of the series. Studies in antifertility agents.

$ArCH_3$), 6.40-6.90 (*m*, 3H, ArH). **4** could also be oxidised by Jone's reagent[6] to the corresponding 2,6β-diethyl-3-(2-methyl-4-methoxyphenyl)bicyclo-[4.3.0]non-2-en-7-one (**6**) (Scheme 1) as an oil; yield 74%; IR(neat); 1740 (C=O); PMR: 2.2 (*s*, 3H, $ArCH_3$) 3.67 (*s*, 3H, OCH_3), 6.5-6.9 (*m*, 3H, ArH).

Compounds **2-6** were assayed for RBA to uterine cytosol estradiol-17β receptors obtained fvom 21-25 day old Charles Foster rats according to the method of Korenman[7] as modified by Katzenellenbogen[8] and the results are listed in Table 1. Antiimplantation activities of these compounds were determined in female albino rats mated with coeval males of proven fertility as described earlier[9] and the results are given in Table 1.

Whereas compounds **3** and **4** prevented implantation in rats at 2 mg/kg, **2** and **5** were only partially effective at this dose. Compound **6** was active at a higher dose of 10 mg/kg.

All the compounds reported above gave correct elemental analyses. The melting points were determined in a sulphuric acid bath and are uncorrected. The IR spectra were taken on a Perkin-Elmer 177 instrument, PMR spectra in $CDCl_3$ on a Perkin Elmer R-32 spectrophotometer using TMS as internal standard and mass spectra on a JMS-Jeol D-300 instrument at 70 eV. Only essential spectroscopic data are presented.

Table 1 – RBA and Antiimplantation Activities

Compd	RBA (%)	Antiimplantation activity, mg/kg (rat)
Estradiol 17β	100	—
2	not detectable	10, 2†
3	0.16 ± 0.03*	2
4	0.14 ± 0.01	2
5	11.30 ± 1.30	10,2†
6	not detectable	10

* Mean ± SEM
† Partially active.

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Synthesis & Antifungal & Antibacterial Activities of Some 5-(Dihydrocinnamoyl)dihydrochalcones

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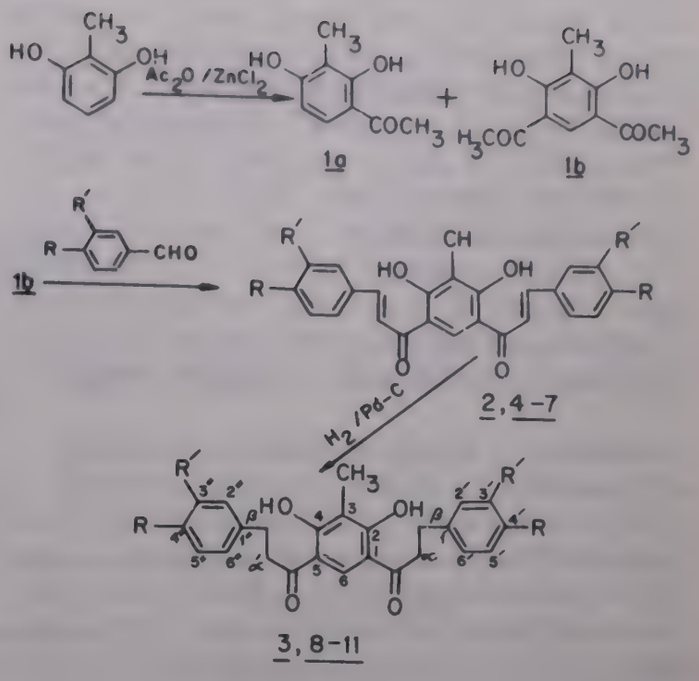
Some 5-(dihydrocinnamoyl)dihydrochalcones (**3**, **8-11**) have been synthesised starting from 1,5-diacetyl-2,4-dihydroxy-3-methylbenzene and screened for their antifungal and antibacterial activities.

Dihydrochalcones are typical precursors of a large group of plant products designated as flavonoids. Many of them and their synthetic analogues are known to possess fungicidal[1], bactericidal[2], antiinflammatory[2] and analgesic[2] activities. Some dihydrochalcones are well known for their sweetening property[3,4] and appear to be non-nutritive sweetners. A dihydrochalcone 'Uvaretin' from *Uvaria acuminata* has shown antitumor activity[5] in lymphocytic leukemia test. Prompted by these activities of dihydrochalcones, we have synthesised some dihydrocinnamoyl substituted dihydrochalcones.

1,5-Diacetyl-2,5-dihydroxy-3-methylbenzene (**1b**), the starting material for the synthesis of various 5-cinnamoylchalcones (dichalcones), was obtained (60%) by the reaction of acetic anhydride and 1,3-dihydroxy-2-methylbenzene in the presence of zinc chloride along with its monoacetyl derivative (**1a**) as a minor product (25%). It was obtained in pure state by crystallisation from methanol. Both the compounds were characterised on the basis of their PMR spectral data. **1a** was identical with 1-acetyl-2,4-dihydroxy-3-methylbenzene[6]. The PMR spectrum of **1b** showed a singlet of six protons at δ 2.62 for two acetyl groups and a singlet at 8.09 for one aromatic proton besides other usual signals for two hydroxyls and one methyl group.

1b on condensation with various substituted benzaldehydes and in presence of ethanolic potassium hydroxide gave the corresponding 5-substituted-cinnamoyl-2,4-dihydroxy-3-methylchalcones (**2** and **4-7**). **2** on hydrogenation in the presence of 5% Pd-C gave the tetrahydro derivative **3** which showed a multiplet at δ 2.87-3.18 for two $-CH_2-CH_2-$ groups in place of α, β-protons of the chalcone moiety. The other dihydrocinnamoyldihydrochalcones (**8-11**) were similarly prepared by reduction of the corresponding chalcones (**4-7**).



2,3 R = H, R′ = H
4,8 R = OCH_3 ; R′ = H
5,9 R = CH_3; R′ = H
6,10 R = OCH ; R′ = OCH_3
7,11 R = R′ = $-O-CH_2-O-$

Biological activity

Compounds **2-11** were screened *in vitro* against the gram-positive *Staphylococcus aureus* and gram-negative *Escherichia coli* at 25 μg/ml and 50 μg/ml concentrations using cup-plate-agar diffusion method[7]. Of these compounds, **6** showed maximum inhibition against *S. aureus* at 25 μg/ml. Rest of the compounds showed marginal activity.

All the compounds were also screened *in vitro* against the fungi *Aspergillus fumigatus* and *Aspergillus niger* at 25 μg/ml and 50 μg/ml concentrations using the modified Czapek Dox nutrient medium[8]. Compound **4** showed nearly 47% inhibition against *A. fumigatus* at 25 μg/ml concentration in comparison to bavistin (standard).

Procedure for one typical case has been described. Melting points are uncorrected and were taken in sulphuric acid bath. IR spectra were recorded on a Perkin-Elmer grating infrared spectrophotometer, model 621 and PMR spectra on a Perkin-Elmer R-32 (90 MHz) spectrometer.

1,5-Diacetyl-2,4-dihydroxy-3-methylbenzene (**1b**)

To a mixture of freshly fused and powdered zinc chloride (1 g) in dry acetic anhydride (1.3 ml) was added

dry 1,3-dihydroxy-2-methylbenzene (1 g) quickly while stirring. The mixture was gently heated on a flame to 142° (15 min). The viscous red solution was allowed to cool to room temperature, and 8 ml of HCl (1 : 1) added to the syrupy mass and stirred. After a few min an orange red crystalline material separated out (1.5 g) which on crystallization from methanol gave **1b** as white needles (1 g, 60%), m.p. 146-47°; IR (KBr) 1640 cm^{-1}; PMR ($CDCl_3$): δ 2.03 (*s*, 3H, CH_3), 2.62 (*s*, 6H, 2 × $-COCH_3$), 8.09 (*s*, 1H, H-6), 13.32 (*s*, 2H, exchangeable with D_2O, 2 × −OH) (Found: C, 63.9; H, 5.5. $C_{11}H_{12}O_4$ requires C, 63.4; H, 5.7%). The mother liquor contained 1,3-dihydroxy-2-methylbenzene and 2,4-dihydroxy-3-methylacetophenone (**1a**; 0.34g, 25%), m.p. 156-57°, identical with an authentic sample[6].

Condensation of **1b** *with benzaldehyde*: *Formation of 5-cinnamoyl-2,4-dihydroxy-3-methylchalcone*(**2**)

To a solution of **1b** (1 g) and benzaldehyde (1.05 ml) in ethanol (20 ml), potassium hydroxide (8 g) was added and the mixture stirred for 6 hr at 35-40°. It was diluted with water (100 ml) and acidified with dil. hydrochloric acid in cold. The solid, thus obtained, was filtered, washed with water and crystallised from ethyl acetate to give **2** as yellow crystals (1.5 g, 82%), m.p. 221-22°; IR (KBr): 1625 cm^{-1}; PMR ($CDCl_3$): δ 2.20 (*s*, 3H, $-CH_3$), 7.30 (*d*, $J = 17$ Hz mixed with *m*, 2H, H-α, H-α'), 7.36-7.70 (*m*, 10H, Ar−*H*), 7.78 (*d*, $J = 17$ Hz, mixed with *m*, 2H, H-β, H-β'), 8.40 (*s*, 1H, H-6), 12.95 (*s*, 2H, exchangeable with D_2O 2 × −OH) (Found: C, 78.5; H, 5.1. $C_{25}H_{20}O_4$ requires C, 78.1, H, 5.2%).

Other dichalcones which were prepared in a similar manner are as follows:

4: m.p. 230-31°, yield 93%.
5: m.p. 225-26°, yield 88%.
6: m.p. 234-35°, yield 82%.
7: m.p. 200-201°, yield 88%.

5-(α',β'-Dihydrocinnamoyl)-2,4-dihydroxy-3-methyl-α,β-dihydrochalcone (**3**)

A solution of **2** (0.5 g) in dry ethyl acetate (25 ml) and abs. ethanol (10 ml), was hydrogenated for 6 hr using Pd−C (5%; 0.4 g) as catalyst. It was filtered, washed with hot ethyl acetate and combined filtrate distilled. The solid thus obtained on crystallisation from benzene-pet. ether afforded **3** as colourless shining needles (0.13 g, 25%), m.p. 101-2°; IR (KBr): 1635 cm^{-1}; PMR ($CDCl_3$): δ 2.05 (*s*, 3H, $-CH_3$), 2.87-3.18 (*m*, 8H, α-H_2, α'-H_2, β-H_2 and β'-H_2), 7.00-7.28 (*m*, 10H, Ar−*H*), 7.85 (*s*, 1H, H-6), 13.14 (*s*, 2H, exchangeable with D_2O, 2 × OH) (Found: C, 71.5; H, 6.2. $C_{25}H_{24}O_4$ requires C, 71.3; H, 6.1%).

Other members of the series prepared similarly are as follows:

8: m.p. 150-51°, yield 35%.
9: m.p. 165-66°, yield 40%.
10: m.p. 154-55°, yield 25%.
11: m.p. 160-61°, yield 40%.

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Synthesis & Biological Activity of 3-(5-Aryl-1,3,4-oxadiazol-2-ylmethyl)-2-methyl-4(3*H*)-quinazolinones

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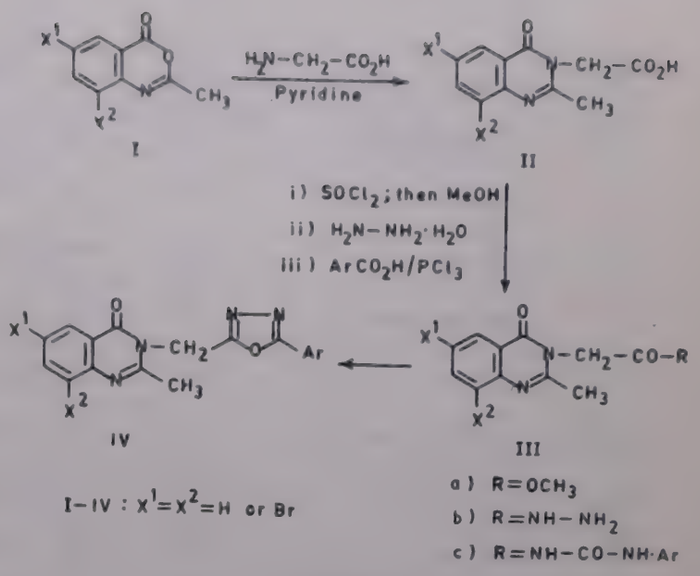
Fourteen 3-(5-aryl-1,3,4-oxadiazol-2-ylmethyl)-2-methyl-4(3*H*)quinazolinones (IV) have been prepared by condensation of the respective 2-methyl-4-oxo-3-quinazolineacetic acid hydrazides with different aromatic carboxylic acids in the presence of phosphorous trichloride, and screened for their antibacterial, antifungal, analgesic and antiinflammatory activities. Some of these compounds have been found to be good analgesic and antiinflammatory agents.

It is evident from literature that both oxadiazoles and quinazolinones are well known for their varied biological activities such as antibacterial[1], antifungal[2], analgesic[3] and antiinflammatory[4]. Therefore, it was felt interesting to bring these two biologically active moieties within a molecular framework with a view to studying their additive effect on biological properties. As a step in this direction and in continuation of our work on 4(3*H*)-quinazolinones[5], the synthesis and biological evaluation of the title compounds were taken up and the results are presented in this note.

The required 2-methyl-4-oxo-3-quinazolineacetic acids (II) were prepared by the condensation of glycine with the respective 2-methyl-3,1,4-benzoxazinones (I). The methyl 2-methyl-4-oxo-3-quinazolinylacetate (IIIa) was obtained by reacting II with thionyl chloride and methanol. Its subsequent reaction with hydrazine hydrate resulted in the formation of 2-methyl-4-oxo-3-quinazolineacetic acid hydrazide (IIIb), earlier prepared by a different method[3]. Compound IIIb on dehydrocyclization with various aromatic carboxylic acids (IV) in the presence of phosphorous trichloride yielded the corresponding 3-(5-aryl-1,3,4-oxadiazol-2-ylmethyl)-2-methyl-4(3*H*)-quinazolinones (IVa-n; Table 1). However, a similar reaction with 4-nitro- or 3,5-dinitrobenzoic acid was found to result in the formation of the corresponding diacylhydrazine (IIIc) only (Scheme 1). The IR spectrum of IIIc showed strong absorptions at 1700 (C=O, amide), 1690 (C=O, arylamide) and 1670 cm^{-1} (C=O, quinazolone). Compound IIIb exhibited IR absorption bands at 3320 and 1690 cm^{-1} for $-NH_2$ and amide C=O whereas the IR spectra of compounds IV showed the absence of these bands, indicating the involvement of



Scheme 1

these two functional groups of IIIb in dehydrocyclization to give IV. The mass spectrum of compound IVh showed the molecular ion at *m/z* 476 and the (P+2) and (P+4) ions characteristic of two bromine atoms. The PMR spectrum of IVa in $CDCl_3$ exhibited signals at δ 2.7 (*s*, 3H, $-CH_3$), 5.5 (*s*, 2H, $-CH_2-$), 7.35-8.0 (*m*, 8H, Ar–*H*) and 8.3 (*d*, 1H, Ar $-C_5H$, J=2 Hz).

Isolation of a diacylhydrazine (IIIc) in the case of nitrobenzoic acid indicates it as an intermediate for its onward dehydrocyclization to give the corresponding oxadiazole (IV).

Biological activity

Compounds IV were evaluated for their antibacterial activity[6] against *B. megaterium* and *E. coli*, antifungal activity[7] against *C. lunata* and *D. haloids*, and analgesic and antiinflammatory activities[8-10] in albino mice and rats respectively. Rifampicin, calixin, aspirin and phenylbutazone were used as standards, respectively. The toxicity studies revealed the LD_{50} values of IV to be very high, ranging from 1500-1800 mg/kg body weight on oral administration. No toxic symptoms were recorded below 1500 mg/kg.

The present compounds in general were found to possess a promising antiinflammatory activity. Compounds IVa, IVd, IVf-i and IVk-m showed moderate protection (40 to 45%) against carrageenin-induced rat-paw oedema, while IVe, IVi and IVn exhibited 50 to 64% inhibition as compared to 58% by phenylbutazone. They too were found to possess a moderate analgesic activity and compound IVm was more potential. However, these compounds were

Table 1—Physical and Analytical Data of 3-(5-Aryl-1,3,4-oxadiazol-2-ylmethyl)-2-methyl-4(3*H*)-quinazolinones (IV)

Compd	Ar	m.p. (°C)	Yield (%)	Mol. formula	Eluant*	Found (%) (Calc.) C	H	N
				$X^1=X^2=H$				
IVa	Phenyl	220	60	$C_{18}H_{14}N_4O_2$	B-C (1:2)	67.7 (67.9	4.3 4.4	17.5 17.6)
IVb	*o*-Chlorophenyl	295	55	$C_{18}H_{13}N_4O_2Cl$	C-EA (2:1)	61.2 (61.4	3.2 3.7	15.7 15.9)
IVc	*p*-Tolyl	275	60	$C_{19}H_{16}N_4O_2$	C-EA (2:1)	68.2 (68.7	4.6 4.8	16.5 16.9)
IVd	*p*-Anisyl	285	55	$C_{19}H_{16}N_4O_3$	B-C (1:1)	65.3 (65.5	4.2 4.6	16.0 16.1)
IVe	*p*-Hydroxyphenyl	>320	50	$C_{18}H_{14}N_4O_3$	C	64.2 (64.7	4.1 4.2	16.4 16.8)
IVf	Benzyl	265	60	$C_{19}H_{16}N_4O_2$	B-C (1:2)	68.4 (68.7	4.6 4.8	16.5 16.9)
IVg	*p*-Chlorophenoxymethyl	292	55	$C_{19}H_{15}N_4O_3Cl$	C-EA (2:1)	59.3 (59.7	3.7 3.9	14.3 14.7)
				$X^1=X^2=Br$				
IVh	Phenyl	230	55	$C_{18}H_{12}N_4O_2Br_2$	C-EA (2:1)	45.2 (45.4	2.4 2.5	11.6 11.8)
IVi	*o*-Chlorophenyl	275	50	$C_{18}H_{11}N_4O_2ClBr_2$	B-C (1:1)	42.2 (42.4	2.0 2.2	10.7 11.0)
IVj	*p*-Tolyl	260	60	$C_{19}H_{14}N_4O_2Br_2$	C	46.2 (46.5	2.7 2.9	11.3 11.4)
IVk	*p*-Anisyl	275	60	$C_{19}H_{14}N_4O_3Br_2$	C-EA (1:1)	44.9 (45.1	2.6 2.8	11.0 11.1)
IVl	*p*-Hydroxyphenyl	290	55	$C_{18}H_{12}N_4O_3Br_2$	B-C (1:2)	43.7 (43.9	2.3 2.4	11.3 11.4)
IVm	Benzyl	270	55	$C_{19}H_{14}N_4O_2Br_2$	EA	46.3 (46.5	2.6 2.9	11.4 11.4)
IVn	*p*-Chlorophenoxymethyl	280	55	$C_{19}H_{13}N_4O_3ClBr_2$	C-EA (1:1)	42.1 (42.2	2.3 2.4	10.2 10.4)

*B = Benzene, C = chloroform and EA = ethyl acetate

shown to be devoid of any antimicrobial activity.

Melting points were determined on a Toshniwal melting point apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer infracord-283 spectrophotometer in nujol mull, 60 MHz PMR spectra on a Varian EM-360, spectrophotometer using TMS as internal reference, and mass spectra on a CEC-2-1110B double focussing spectrometer.

3,5-Dibromoanthranilic acid and 2-methyl-3,1,4-benzoxazinones (I) were prepared by the method of Wheeler and Oats[11].

2-Methyl-4-oxo-3-quinazolineacetic acid (IIa; $x^1=x^2=H$)

A mixture of $IIIa_1$ (23.2 g, 0.1 mol) and hydrazine mol) in aq. pyridine (25 ml of pyridine in 50 ml of water) was refluxed for 6 hr, pyridine distilled off to the possible extent and the residue digested with 1*N* hydrochloric acid (200 ml) for 2 hr on a water-bath. The solid thus obtained was filtered, washed with small portions of cold water and recrystallised from ethanol to get II as a colourless crystalline substance (17.44 g; 80%), m.p. 260°. IR: 2750 (−OH, carboxylic), 1700 (C=O, carboxylic), 1680 cm^{-1} (C=O, quinazolone) (Found: C, 60.3; H, 4.9; N, 12.8. $C_{11}H_{10}N_2O_3$ requires C, 60.6; H, 4.6; N, 12.8%).

6,8-Dibromo-2-methyl-4-oxo-3-quinazolineacetic acid (IIb; $X^1=X^2=Br$) was prepared in a similar way from 6,8-dibromobenzoxazin-4-one (I; $X^1=X^2=Br$), yield 75%, m.p. 230° (Found: C, 35.0; H, 2.1; N, 7.4. $C_{11}H_8N_2O_3Br_2$ requires C, 35.1; H, 2.1; N, 7.4%).

Methyl 2-methyl-4-oxo-3-quinazolinyl-acetates (IIIa; $X^1=X^2=H$, Br)

Compound IIa (10.9 g; 0.05 mol) was refluxed with excess of thionyl chloride (15 ml) in analar methanol (75 ml) for 4-5 hr. The mixture was cooled and neutralised with sodium carbonate. The product ($IIIa_1$; $X^1=X^2=H$) formed was filtered, washed with cold water and dried, yield 65%, m.p. 135°; IR: 1730 (O=C−OCH_3), 1680 cm^{-1} (C=O, quinazolone) (Found: C, 62.6; H, 5.0; N, 12.0. $C_{12}H_{12}N_2O_3$ requires

C, 62.1; H, 5.2; N, 12.1%).

Methyl 6,8-dibromo-2-methyl-4-oxoquinazolin-3-ylacetate ($IIIa_2$; $X^1=X^2=Br$) was prepared in a similar manner from IIb, yield 65%, m.p. 175° (Found: C, 36.8; H, 2.5; N, 7.1. $C_{12}H_{10}N_2O_3Br_2$ requires C, 36.9; H, 2.6; N, 7.2%).

2-Methyl-4-oxo-3-quinazolineacetic acid hydrazides (*IIIb*; $X^1=X^2=H$, *Br*)

A mixture of $XIIIa_1$ (23.2 g, 0.1 mol) and hydrazine-hydrate (10.0 g, 99%, 0.2 mol) in methanol (150 ml) was refluxed for 3 hr, cooled and the resultant solid filtered, washed with small portions of cold water and recrystallised from ethanol to get $IIIb_1$ as a colourless crystalline compound, yield 75%, m.p. 260° (lit.[3], m.p. 260°); IR: 3340, 3200 ($-NHNH_2$), 1690 (O=C, amide), 1670 cm^{-1} (O=C, quinazolone); PMR(CCl_4): δ 2.52 (*s*, 3H, $-CH_3$), 5.35 (*s*, 2H, $-CH_2-$), 4.8 (broad, 2H, $-NH_2$ exchangeable with D_2O), 7.2-7.7 (*m*, 3H, Ar−*H*), 8.21 (*d*, 1H, Ar−C_5H, $J=2$ Hz) and 9.5 (*s*, 1H, NH, exchangeable with D_2O) (Found: C, 57.0; H, 5.3; N, 24.3. Calc. for $C_{11}H_{12}N_4O_2$: C, 56.9; H, 5.2; N, 24.1%).

In a similar way 6,8-dibromo-2-methyl-4-oxo-3-quinazolineacetic acid hydrazide ($IIIb_2$; $X^1=X^2=Br$) was prepared from $IIIa_2$, yield 70%, m.p. 285° (lit.[3], m.p. 285).

3-(5-Aryl-1,3,4-oxadiazol-2-ylmethyl)-2-methyl-4(3H)-quinazolinones (*IV*):
General procedure

A mixture of IIIb (0.005 mol), aromatic carboxylic acid (0.005 mol) and phosphorous trichloride (13 ml, 0.1 mol) in dry benzene (20 ml) was refluxed under anhydrous conditions for 4-5 hr. Benzene was distilled off under reduced pressure, and the residue poured onto crushed ice and neutralized with sodium bicarbonate. The solid thus obtained was filtered, washed with cold water and purified over a column of alumina (neutral) using suitable solvents as eluant (Table 1).

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Synthesis & Insecticidal Activity of Some New Phosphorodithioate Esters of Substituted Acetophenones

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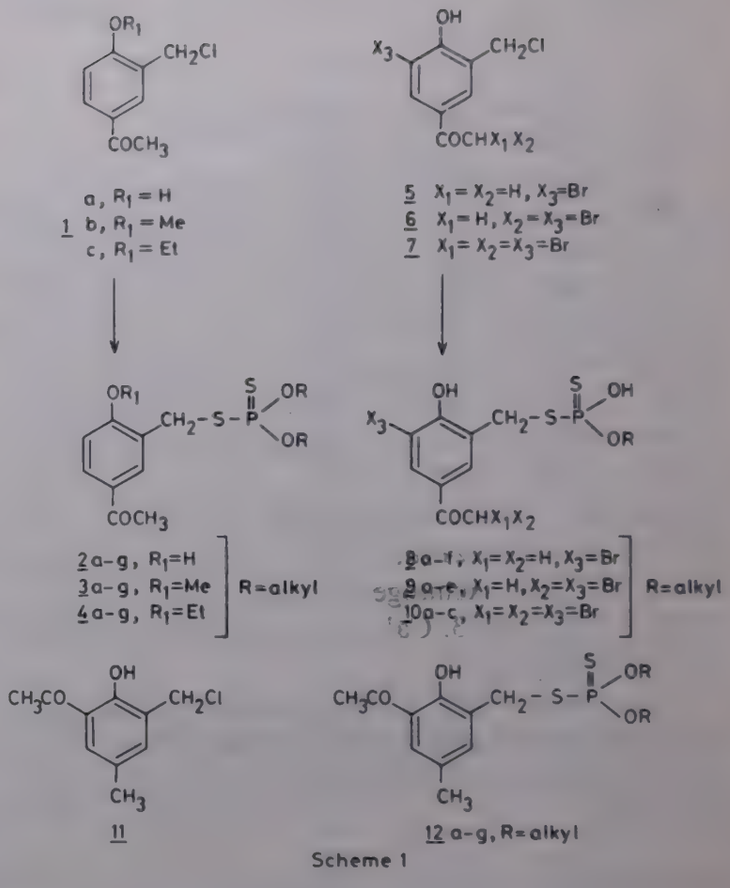
A number of new phosphorodithioate esters (**2-4, 8-10, 12**) derived from 5-acetyl-2-hydroxy/methoxy/ethoxy-benzyl chlorides (**1a-c**), 5-acetyl/5-(ω-bromoacetyl)/5-(ω, ω-dibromoacetyl)-3-bromo-2-hydroxybenzyl chlorides (**5-7**) and 3-acetyl-2-hydroxy-5-methylbenzyl chloride (**11**) have been synthesised and screened for their insecticidal activity. Methanolysis of compounds **2-4** has also been studied in the presence of triethylamine.

Several phosphorodithioate group of organophosphorus compounds are known to have significant insecticidal activity[1]. In view of the importance of this class of compounds and in continuation of our work on organophosphorus compounds having substituted acetophenone nucleus[2,3], it was thought of interest to synthesise some new O, O-dialkylphosphorodithioic acid esters having acetophenone or substituted acetophenone nucleus and test their insecticidal activity. The base-catalysed degradation of these compounds was also studied.

The starting material 5-acetyl-2-hydroxybenzyl chloride (**1a**) and its 2-methoxy and 2-ethoxy derivatives (**1b, c**) were prepared by the method of Trave[4]. 5-Acetyl-3-bromo-2-hydroxybenzyl chloride (**5**) was prepared by brominating **1a** with 1 mol of bromine in methanol and methylene chloride in cold condition. The other two bromo compounds, 5-(ω-bromoacetyl)- and 5-(ω, ω-dibromoacetyl)-3-bromo-2-hydroxybenzyl chlorides (**6, 7**) were prepared by carrying out the bromination of **1a** at room temperature with two and three mol of bromine respectively. Condensation of these compounds (**1, 5, 6, 7**) with appropriate O, O-dialkylphosphorodithioates in dry benzene in the presence of anhyd. potassium carbonate under reflux gave the desired esters (**2-4** and **8-10**). The hydroxy derivatives gave better yields when these were warmed with almost neutral potassium salts of phosphorodithioic acids in aq. medium. The dithioesters (**12**; Table 1) of 2-hydroxy-3-acetyl-5-methylbenzyl chloride (**11**) were also synthesised in a similar way. The above reactions are shown in Scheme 1.



Scheme 1

Compounds **2** underwent alcoholic degradation when subjected to methanolysis in the presence of triethylamine. The compounds with a phenolic group *ortho* to benzylic dithiophosphate ester group (**2a-g**) readily decomposed to compound **16** and dialkyl hydrogenphosphorodithioate as trimethylammonium salt (**14**) which on methylation with methyl iodide and purification gave O, O-dialkyl-S-methylphosphorothionothiolate (**15**; Scheme 2). The structure **15** was supported by the appearance of a characteristic IR absorption at 650 cm^{-1} due to P=S stretching[6] and a PMR doublet for $P-S-CH_3$ protons at δ 2.33 with a $^3J_{P-H}$ value[7] of 16 Hz. However, the compounds having a 6-methoxy or 6-ethoxy group (**3a-g, 4a-g**) did not undergo such a degradation even after refluxing the reaction mixture for more than 36 hr. These observations indicate participation of the hydroxyl group via the proposed intermediate **13** as shown in Scheme 2.

The PMR spectra of all the phosphorodithioate esters (**2-4, 8-10** and **12**) exhibited a general ^{31}P nucleus coupled resonance of reported $^3J_{P-S-CH_2}$ value of 14-16 Hz. For example, the methylene protons of the

Table 1—Characterization and Insecticidal Activity Data of Various Compounds Prepared

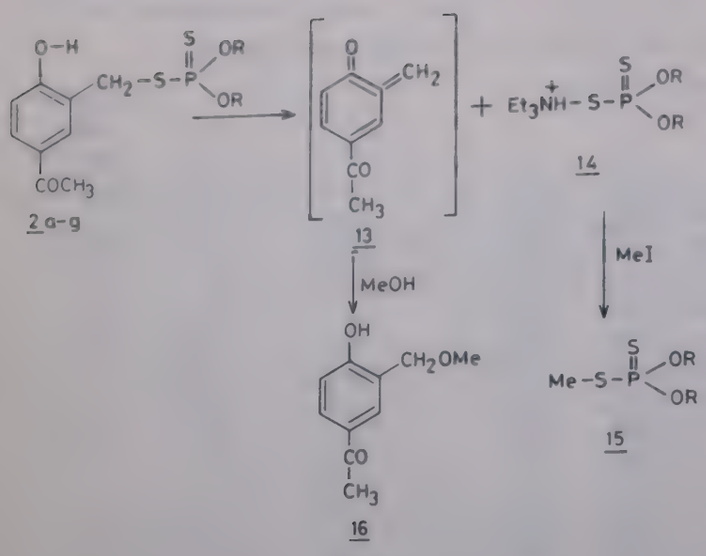
Compd	R	m.p. °C	Yield (%)	Mol. formula (M^+)		S (%) Found	S (%) Calc.	Insecticidal activity*
2a	Methyl	85-87	80	$C_{11}H_{15}O_4PS_2$	(306)	20.7	20.9	+
2b	Ethyl	110-112	95	$C_{13}H_{19}O_4PS_2$	(334)	19.4	19.2	+ + +
2c	Propyl	Oil	96	$C_{15}H_{23}O_4PS_2$	(362)	18.0	17.7	+ +
2d	Isopropyl	88-90	85	$C_{15}H_{23}O_4PS_2$	(362)	17.5	17.7	+ + +
2e	Butyl	Oil	90	$C_{17}H_{27}O_4PS_2$	(390)	16.7	16.4	—
2f	Isobutyl	Oil	75	$C_{17}H_{27}O_4PS_2$	(390)	16.7	16.4	—
2g	Isoamyl	Oil	80	$C_{19}H_{33}O_4PS_2$	(418)	15.5	15.3	—
3a	Methyl	Oil	60	$C_{12}H_{17}O_4PS_2$	(320)	19.9	20.0	+ + +
3b	Ethyl	Oil	70	$C_{14}H_{21}O_4PS_2$	(348)	18.1	18.4	+ + +
3c	Propyl	Oil	60	$C_{15}H_{25}O_4PS_2$	(376)	17.2	17.0	+ + +
3d	Isopropyl	Oil	65	$C_{15}H_{25}O_4PS_2$	(376)	17.2	17.0	+
3e	Butyl	Oil	50	$C_{18}H_{29}O_4PS_2$	(404)	16.0	15.8	+ +
3f	Isobutyl	Oil	70	$C_{18}H_{29}O_4PS_2$	(404)	15.6	15.8	—
3g	Isoamyl	Oil	75	$C_{20}H_{33}O_4PS_2$	(432)	14.5	14.8	—
4a	Methyl	Oil	75	$C_{13}H_{19}O_4PS_2$	(334)	19.4	19.2	+
4b	Ethyl	Oil	80	$C_{15}H_{23}O_4PS_2$	(362)	17.9	17.7	—
4c	Propyl	Oil	70	$C_{17}H_{27}O_4PS_2$	(390)	16.2	16.4	—
4d	Isopropyl	Oil	65	$C_{17}H_{27}O_4PS_2$	(390)	16.5	16.4	—
4e	Butyl	Oil	70	$C_{19}H_{31}O_4PS_2$	(418)	15.5	15.3	—
4f	Isobutyl	Oil	60	$C_{19}H_{31}O_4PS_2$	(418)	15.1	15.3	—
4g	Isoamyl	Oil	60	$C_{21}H_{35}O_4PS_2$	(446)	14.0	14.3	+
5	—	120	85	$C_9H_8O_2ClBr$	(263)	—	—	—
6	—	95	80	$C_9H_7O_2ClBr_2$	(342)	—	—	—
7	—	140	82	$C_9H_6O_2ClBr_3$	(421)	—	—	—
8a	Methyl	Oil	80	$C_{11}H_{14}O_4BrS_2P$	(385)	16.6	16.3	+ + +
8b	Ethyl	Oil	82	$C_{13}H_{18}O_4BrS_2P$	(413)	15.5	15.7	+ + +
8c	Propyl	Oil	85	$C_{15}H_{22}O_4BrS_2P$	(441)	14.5	14.6	—
8d	Butyl	Oil	80	$C_{17}H_{26}O_4BrS_2P$	(469)	13.6	13.8	—
8e	Isobutyl	Oil	83	$C_{19}H_{28}O_4BrS_2P$	(469)	13.6	13.4	—
8f	Isoamyl	Oil	82	$C_{19}H_{30}O_4BrS_2P$	(497)	12.9	13.2	—
9a	Methyl	Oil	65	$C_{11}H_{13}O_4Br_2S_2P$	(464)	13.8	13.5	+
9b	Ethyl	Oil	75	$C_{13}H_{17}O_4Br_2S_2P$	(492)	13.0	13.3	+
9c	Propyl	Oil	80	$C_{15}H_{21}O_4Br_2S_2P$	(520)	12.3	12.5	+
9d	Butyl	Oil	75	$C_{17}H_{25}O_4Br_2S_2P$	(548)	11.7	12.0	+
9e	Isoamyl	Oil	71	$C_{19}H_{29}O_4Br_2S_2P$		11.1	11.3	+
10a	Methyl	Oil	75	$C_{11}H_{12}O_4Br_3S_2P$	(543)	11.8	12.1	+ +
10b	Ethyl	Oil	80	$C_{13}H_{16}O_4Br_3S_2P$		11.2	11.0	+ + +
10c	Isopropyl	Oil	76	$C_{15}H_{20}O_4Br_3S_2P$		10.7	10.9	+ + +
12a	Methyl	100	80	$C_{12}H_{17}O_4S_2P$	(320)	20.0	22.2	+
12b	Ethyl	Oil	85	$C_{14}H_{21}O_4S_2P$	(348)	18.4	18.2	+
12c	Propyl	Oil	70	$C_{16}H_{25}O_4S_2P$	(376)	17.0	16.9	+ +
12d	Isopropyl	Oil	73	$C_{16}H_{25}O_4S_2P$	(376)	17.0	17.3	—
12e	Butyl	Oil	82	$C_{18}H_{29}O_4S_2P$	(404)	15.8	16.0	+ +
12f	Isobutyl	Oil	84	$C_{18}H_{29}O_4S_2P$	(404)	15.8	15.6	+ + +
12g	Isoamyl	Oil	76	$C_{20}H_{33}O_4S_2P$	(432)	14.8	15.0	—

*Mortality up to 50 = +, 51-70 = + +, 71-100 = + + +

benzylic dithiophosphate ester group appeared as a doublet with a $^3K_{P-S-CH_2}$ value of 15-16 Hz. Interestingly, the ring methoxy methyl and ethoxy methylene protons and the *ortho* ring proton (H-3) showed large up-field chemical shifts when the PMR solvent was changed from an isotropic ($CHCl_3$) to an anisotropic solvent (benzene). The upfield shifts for these compounds indicate some type of steric interaction between the ortho-aromatic (H-3) and the O-methyl or O-methylene protons induced by the solvent benzene by packing closely around the positively charged ring alkoxy oxygen atom[8,9] in a more stabilized *p*-quinoid structure[10] for these compounds (**3a-g** and **4a-g**). The structural assignments of the compounds were based on elemental analyses and spectral data.

Insecticidal activity

All the organophosphorus compounds were evaluated for their insecticidal activity against



Scheme 2

Drosophila melanogaster (Vinegar fly) by standard method[11] at 0.2-1% concentration. The mortality was observed after 24 hr. Among the compounds tested, only compounds **8a**, **b**, **10b**, **c** and **12f** exhibited the insecticidal activity of a high order. Rest of the compounds showed either moderate or no activity (Table 1).

IR spectra (ν_{max} in cm^{-1}) were recorded on a Perkin-Elmer 237B spectrophotometer, PMR spectra (chemical shift in δ, ppm) on a Varian T-60 instrument using TMS as internal standard and mass spectra on an AEI MS 30 instrument.

5-Acetyl-3-bromo-2-hydroxybenzyl chloride (**5**)

To a stirred solution of 5-acetyl-2-hydroxybenzyl chloride (**1a**[1]; 5 g) in methanol (3 ml) and dichloromethane (30 ml) was added bromine (4.5 g) in dichloromethane (20 ml) dropwise at 0°. After 1 hr, excess of bromine was decomposed with sodium metabisulphite solution, the dichloromethane layer separated and the aq. layer extracted with dichloromethane. The combined methylene chloride extract was washed with water, dried, solvent removed and the residue crystallized from benzene to give **5**, yield 6.1 g (85%), m.p. 120-21°; IR 1675 (CO), 3200 (OH); PMR ($CDCl_3$): 2.55 (*s*, 3H, $COCH_3$), 4.7 (*s*, 2H, $Ar-CH_2$), 8.0 (*q*, 2H, $Ar-H$) (Found: Br, 30.2. $C_9H_8O_2ClBr$ requires Br, 30.4%).

3-Bromo-5-(ω-bromoacetyl)-2-hydroxybenzyl chloride (**6**)

To a stirred solution of **1a** (5 g) in methanol (5 ml) and CH_2Cl_2 (50 ml) was added bromine (9 g in 50 ml CH_2Cl_2) dropwise at room temperature during 3 hr. Excess of bromine was decomposed, the organic layer separated and washed thoroughly with water, dried and solvent removed to afford a solid which on crystallization from benzene gave **6**, yield 7.4 g (80%), m.p. 95°; IR: 1675 (CO), 3250 (OH); PMR ($CDCl_3$): 4.37 (*s*, 2H, $Ar-CH_2$), 4.7 (*s*, 2H, $COCH_2$), 8.2 (*q*, 2H, $Ar-H$) (Found: Br, 46.5. $C_9H_7O_2ClBr_2$ requires Br, 46.8%).

3-Bromo-5-(ω, ω-dibromoacetyl)-2-hydroxybenzyl chloride (**7**)

The same procedure was followed to prepare **7** as described for **6** except 3 mol (13.5 g) of bromine were added instead of 2 mol. The usual work-up afforded **7**, yield 9.3 g (82%), m.p. 140°; IR: 1665 (CO), 3200 (OH); PMR ($CDCl_3$): 4.72 (*s*, 2H, $Ar-CH_2$), 6.52 (*s*, H, $-CO-CH$), 8.2 (*q*, 2H, $Ar-H$) (Found: Br, 57.2. $C_9H_6O_2ClBr_3$ requires Br, 57.0%).

O, O-Dimethyl-S-(3-acetyl-6-methoxybenzyl)-phosphorodithioate (**3a**)

A mixture of **1b** (0.005 mol), anhyd. potassium carbonate (0.64 g, 0.005 mol) and O, O-dimethyl-phosphorodithioic acid (0.01 mol) in dry benzene as refluxed on a water-bath for 2-3 hr, cooled, filtered and the residue washed thrice with benzene. The combined filterate was washed twice with water to remove inorganic impurities, dried (anhyd. Na_2SO_4), solvent removed under reduced pressure, and the residue purified by column chromatography to give **3a** as colourless oil, yield 60%; IR (film): 1680 (CO), 650 (P=S); PMR ($CDCl_3$): 2.27 (*s*, 3H, $COCH_3$), 3.48 (*d*, 6H, $J=16$ Hz, $2\times$ P-OCH_3), 3.77 (*s*, 3H, $ArOCH_3$), 3.80 (*d*, 2H, $J=16$ Hz, $ArCH_2SP$), 6.70 (*d*), 7.70 (*dd*) and 7.77 (d) (3H, $Ar-H$); M^+ 320 (Found: S, 19.9. $C_{12}H_{17}O_4S_2P$ requires S, 20.0%).

Other compounds given in Table 1 were prepared in a similar way.

O, O-Dimethyl-S-(3-acetyl-2-hydroxy-5-methylbenzyl)phosphorodithioate (**12a**)

Same procedure as described for **3a** was used for the preparation of this compound and other compounds of the series (**12b-g**), starting from 3-acetyl-2-hydroxy-5-methylbenzyl chloride, m.p. 100°; IR: 1637, 1190; PMR ($CDCl_3$), 2.43 (*s*, 3H, $COCH_3$), 3.86 (2H, *d*, $J=14.4$ Hz, $Ar-CH_2$), 7.3 (1H, *s*, Ar-4-*H*), 7.3 (1H, *s*, Ar-6-*H*), 12.06 (*s*, *br*, $Ar-OH$); M^+ 320 (Found: S, 19.80. $C_{12}H_{17}O_4S_2P$ requires 20.0%).

Methanolysis of O, O-dialkyl-S-(3-acetyl-6-hydroxybenzyl)phosphorodithioates (**2a-g**)

A mixture of **2b** (0.5 mmol), methanol (7 ml) and triethylamine (1 mmol) was refluxed on a water-bath for 0.5 hr. The reaction mixture was concentrated and the resulting mass purified by preparative TLC (silica gel) using ethyl acetate-benzene (1:3) as solvent system

to get **16** (m.p. 86°) and **14** as triethylammonium salt of O, O-diethylphosphodithioic acid. The compound **16** was found to be identical in all respect (m.m.p. and superimposable IR) with authentic 4-hydroxy-3-methoxymethylacetophenone.

Methylation of triethylammonium salt (**14**) *to O, O-diethyl-S-methylphosphorodithioate* (**15**)

To a solution of **14** (80 mg) in dry chloroform was added few drops of methyl iodide (100 mg) at room temperature and the mixture left overnight. The solvent was distilled off and the residue extracted with hexane, washed with water and dried. Removal of solvent gave the neutral triester **15** as a syrupy oil, identical with authentic O, O-diethyl-S-methylphosphorodithioate.

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2,4-Bis(substituted cinnamoyl/pyrazol-3-yl)phenoxyacetic Acid Esters & Hydrazides as Potential Antimicrobial Agents

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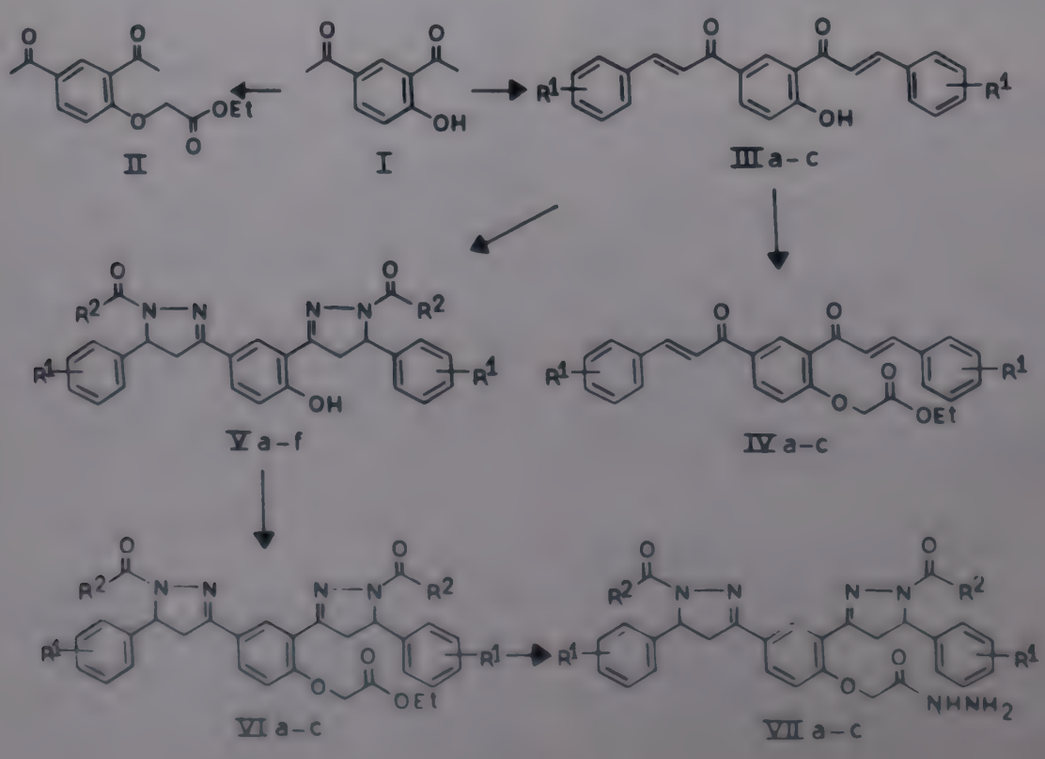
Condensation of 2,4-diacetylphenol (I) with substituted benzaldehydes give 2,4-bis(substituted cinnamoyl)phenols (IIIa-c) which on treatment with hydrazine hydrate in acetic or formic acid furnish the corresponding 2,4-bis(1-acetyl/formyl-4,5-dihydro-5-arylpyrazol-3-yl)phenols (Va-f). Alkylation of I, IIIa-c and Va-c with ethyl chloroacetate gives the corresponding ethyl substituted phenoxyacetates (II, IVa-c and VIa-c). Treatment of VIa-c with hydrazine hydrate in ethanol affords the corresponding hydrazides VIIa-c. None of the compounds tested shows any *in vitro* growth inhibitory activity against *Alternaria alternata*, *Macrophomina phaseolina*, *Helminthosporium oryzae* and *Fusarium oxysporum* upto a concentration of 100 μg/ml.

Substituted 3,5-diarylpyrazoles[1-3], benzopyrano[4,3-*c*]pyrazoles[4,5], benzocycloalkapyrazoles[4] and pyrazolo[4,3-*c*]quinolines[4-6], have been found to exhibit antifertility, antimicrobial and CNS/CVS activities. In view of the reports that acid hydrazides are associated with antimicrobial and antitubercular activities[7,8], it appeared promising to incorporate this unit in such systems. Herein, we report the synthesis and antimicrobial screening results of 2,4-bis(substituted cinnamoyl/pyrazol-3-yl)phenoxyacetic acid esters and hydrazides.

The starting 2,4-diacetylphenol (I) was prepared by acetylation of 4-hydroxyacetophenone followed by Fries' rearrangement of resulting 4-acetylphenyl acetate with aluminium chloride. Alkylation of I with ethyl chloroacetate afforded ethyl 2,4-diacetylphenoxyacetate (II) in quantitative yield. Condensation of I with substituted benzaldehydes furnished the corresponding 2,4-bis(substituted cinnamoyl)phenols (IIIa-c) which on alkylation with ethyl chloroacetate gave ethyl 2,4-bis(substituted cinnamoyl)phenoxyacetates (IVa-c). Refluxing of IIIa-c with hydrazine hydrate in acetic or formic acid furnished the corresponding 2,4-bis(1-acetyl/formyl-4,5-dihydro-5-arylpyrazol-3-yl)phenols (Va-f). The C-4 and C-5 protons of pyrazole ring in Va-f exhibited characteristic chemical shifts and splitting pattern[1-3,9,10] in their PMR spectra.

Treatment of Va-c with ethyl chloroacetate in the presence of potassium carbonate in dimethylformamide furnished the corresponding substituted 2,4-bis(pyrazol-3-yl)phenoxyacetic acid ethyl esters (VIa-c), which on refluxing with hydrazine hydrate in



SCHEME 1

ethanol furnished the corresponding 2,4-bis(pyrazol-3-yl)phenoxyacetic acid hydrazides (VIIa-c) in good yields (Scheme 1).

All the compounds were fully characterised by their IR, PMR spectral and analytical data.

Antimicrobial activity

Five representative compounds, IIIc, IVc, Vc, VIc and VIIc, were tested for their *in vitro* growth inhibitory activity against different strains of fungi, viz. *Alternaria alternata*, *Macrophomina phaseolina*, *Helminthosporium oryzae* and *Fusarium oxysporum*, selected on the basis of their economic importance. These fungi were maintained on Czepex Dox agar slants[11] and testing was carried out in Czepex Dox both by two-fold serial dilution technique[2] by dissolving the compounds in ethanol. All the compounds were ineffective in inhibiting the growth of the fingi upto a concentration of 100 μg/ml.

Melting points were determined in capillary tubes on a Ganson electrical melting point apparatus and are uncorrected. Homogeneity of the compounds was routinely checked on silica gel-G TLC plates using benzene or benzene-methanol mixture as mobile phase. The IR spectra were run on a Perkin-Elmer IR spectrophotometer model 157 (ν_{max} in cm^{-1}) and PMR spectra on a Varian EM-390 90 MHz spectrometer in $CDCl_3$ using TMS as an internal reference; chemical shifts are expressed in δ-scale. All compounds were analyzed for C, H and N and the values were found to be within $\pm 0.4\%$ of the calculated values.

All the compounds showed expected spectral characteristics. Only those spectral data which have a direct bearing on structural assignment have been mentioned. The preparations described below are illustrative of the general methods of the synthesis empolyed. The characterization data of various compounds (Scheme 1) are described in Table 1.

Table 1—Characterization Data of 2,4-Bis(substituted cinnamoyl)/pyrazol-3-yl)phenoxyacetic Acid Esters and Hydrazides

Compd*	R^1	m.p. (°C)	Mol. formula
IIIa	H	132	$C_{24}H_{18}O_3$
		(lit.[13] 135)	
IIIb	3-OCH_3	122	$C_{26}H_{22}O_5$
IIIc	4-OCH_3	142	$C_{26}H_{22}O_5$
IVa	H	124	$C_{28}H_{24}O_5$
IVb	3-OCH_3	138	$C_{30}H_{28}O_7$
IVc	4-OCH_3	156	$C_{30}H_{28}O_7$
		$R^2=CH_3$	
Va	H	122	$C_{28}H_{26}N_4O_3$
Vb	3-OCH_3	108	$C_{30}H_{30}N_4O_3$
Vc	4-OCH_3	118	$C_{30}H_{30}N_4O_3$
		$R^2=H$	
Vd	H	124	$C_{26}H_{22}N_4O_3$
Ve	3-OCH_3	110	$C_{28}H_{26}N_4O_3$
Vf	4-OCH_3	112	$C_{28}H_{26}N_4O_3$
		$R^2=CH_3$	
VIa	H	80	$C_{32}H_{32}N_4O_3$
VIb	3-OCH_3	81	$C_{34}H_{36}N_4O_3$
VIc	4-OCH_3	84	$C_{34}H_{36}N_4O_3$
VIIa	H	139	$C_{30}H_{30}N_4O_3$
VIIb	3-OCH_3	127	$C_{32}H_{34}N_6O_6$
VIIc	4-OCH_3	152	$C_{32}H_{34}N_6O_6$

*All the compounds were obtained in very good yields (>80%).

2,4-*Diacetylphenol* (*I*)

A mixture containing 4-hydroxyacetophenone (27.2 g, 0.2 mol) and acetic anhydride (35 ml) was refluxed for 2 hr. Usual work-up of the reaction mixture afforded 4-acetylphenyl acetate, yield 32 g (90%).

A mixture of 4-acetylphenyl acetate (17.8 g, 0.1 mol) and aluminium chloride (46.7 g, 0.35 mol) was heated at 150°C for 3 hr. The reaction mixture was cooled and decomposed below 15°C by slow addition of dilute HCl. The separated yellow solid was filtered, washed with water and dried to give I, yield 14.2 g (80%); m.p. 92° (lit.[12] m.p. 92-93°).

Ethyl 2,4-*diacetylphenoxyacetate* (*II*)

A mixture of I (1.78 g, 0.01 mol), ethyl chloroacetate (1.34 g, 0.011 mol), potassium carbonate (1.5 g, 0.011 mol) and dimethylformamide (10 ml) was stirred for 20 hr, poured into ice-water and the separated solid was filtered and dried. The product was purified by passing it through a small band of silica using benzene as eluent, yield 2.4 g (90%), m.p. 84°; PMR: 1.30 (*t*, 3 H, $CO_2CH_2CH_3$, $J=7$ Hz), 2.60 (*s*, 3H, $COCH_3$), 2.75 (*s*, 3H, $COCH_3$), 4.30 (*q*, 2H, CO_2CH_2, $J=7$ Hz), 4.83 (*s*, 2 H, OCH_2CO_2), 6.93 (*d*, 1 H, C_6-H, $J=9$ Hz), 8.17 (*dd*, 1 H, C_5-H, $J=2$ and 9 Hz), 8.43 (*d*, 1 H, C_3-H, $J=2$ Hz) (Found: C, 63.9; H, 5.9. $C_{14}H_{16}O_5$ requires C, 63.6; H, 6.1%).

2,4-*Bis*(4-*methoxycinnamoyl*)*phenol* (*IIIc*)

To a cooled (15°) and stirred solution of potassium hydroxide (1.68g, 0.03mol) in methanol (10ml) was added I (1.78 g, 0.01 mol) and 4-methoxybenzaldehyde (2.72 g, 0.02 mol). The reaction mixture was stirred for 48 hr at 25°C and neutralized with dilute sulphuric acid. The precipitated solid was filtered and crystallized from methanol to get IIIc, yield 3.5 g (85%), m.p. 142°; IR: 1660 (C=O), 1615 (C=O, H-bonded); PMR: 3.98 (*s*, 6H, 2 × OCH_3), 7.33-8.37 (comlex *m*, 12H, arom-H and olefinic H), 8.83 (*d*, 1 H, C_3-H, $J=2$ Hz), 13.60 (*bs*, 1H, OH, D_2O exchangeable) (Found: C, 75.5; H, 5.1. $C_{26}H_{22}O_5$ requires C, 75.4; H, 5.4%).

Ethyl 2,4-bis(4-methoxycinnamoyl)phenoxyacetate (IVc)

A mixture of IIIc (0.83 g, 0.002 mol), ethyl chloroacetate (0.27 g, 0.0022 mol), potassium carbonate (0.3 g, 0.0022 mol) and dimethylformamide (5 ml) was stirred for 20 hr. Work-up of the reaction mixture as described for II gave IVc, yield 0.87 g (87%), m.p. 156°; PMR: 1.27 (*t*, 3H, $CO_2CH_2CH_3$, $J = 7$ Hz), 3.87 (*bs*, 6H, $2 \times OCH_3$), 4.27 (*q*, 2H, CO_2CH_2, $J = 7$ Hz), 4.82 (*s*, 2H, OCH_2CO_2) (Found: C, 72.3; H, 5.9. $C_{30}H_{28}O_7$ requires C, 72.0; H, 5.6%).

2,4-Bis[1-acetyl-4,5-dihydro-5-(4-methoxyphenyl)-pyrazol-3-yl]phenol (Vc)

A solution of IIIc (1.04 g, 0.0025 mol) in gl acetic acid (10 ml) was refluxed with hydrazine hydrate (1 ml, excess) for 6 hr. The reaction mixture was cooled, poured onto ice, the separated solid filtered, washed with water, dried and crystallized from methanol to give Vc, yield 1.2 g (91%), m.p. 118°; IR: 3250 (OH), 1675 (C=O); PMR: 2.43 (*s*, 6H, $2 \times OCH_3$), 2.90-4.20 (*m*, 4H, pyrazolyl $2 \times C_4$-H_2), 3.83 (3H, OCH_3), 3.87 (*s*, 3H, OCH_3), 5.62 (*bdd*, 2H, pyrazolyl $2 \times C_5$-H, $J = 5$ and 12 Hz), 7.23-7.90 (*m*, 11H, arom-H), 10.67 (*s*, 1H, OH, D_2O exchangeable) (Found: C, 68.3; H, 5.6; N, 10.9. $C_{30}H_{30}N_4O_5$ requires C, 68.4; H, 5.7; N, 10.6%).

2,4-Bis[1-formyl-4,5-dihydro-5-(4-methoxyphenyl)-pyrazol-3-yl]phenol (Vf)

This was prepared in 92% yield from IIIc using the method described for the preparation of Vc using formic acid instead of acetic acid, m.p. 112°; IR: 3250 (OH), 1678 (C=O); PMR: 3.03-4.20 (*m*, 4H, pyrazolyl $2 \times C_4$-H_2), 3.83 (*s*, 6H, $2 \times OCH_3$), 5.63 (*m*, 2H, pyrazolyl $2 \times C_5$-H), 6.90-7.83 (*m*, 11H, arom-H), 9.03 (*s*, 1H, CHO), 9.07 (*s*, 1H, CHO), 9.07 (*s*, 1H, CHO), 10.53 (*s*, 1H, OH, D_2O exchangeable) (Found: C, 67.5; H, 5.0; N, 11.6. $C_{28}H_{26}N_4O_5$ requires C, 67.5; H, 5.3; N, 11.2%).

Ethyl 2,4-bis[1-acetyl-4,5-dihydro-5-(4-methoxyphenyl)pyrazol-3-yl)]phenoxyacetate (VIc)

Alkylation of Vc using the procedure described for the preparation of II gave VIc in 78% yield, m.p. 84°; PMR: 1.27 (*t*, 3H, $CO_2CH_2CH_3$, $J = 7$ Hz), 2.43 (*s*, 3H, $COCH_3$), 2.47 (*s*, 3H, $COCH_3$), 3.87 (*s*, 6H, $2 \times OCH_3$), 4.32 (*q*, 2H, CO_2CH_2, $J = 7$ Hz), 4.77 (*s*, 2H, OCH_2CO_2) (Found: C, 66.3; H, 6.1; N, 9.4. $C_{34}H_{36}N_4O_7$ requires C, 66.7; H, 5.9; N, 9.2%).

2,4-Bis[1-acetyl-4,5-dihydro-5-(4-methoxyphenyl)-pyrazol-3-yl]phenoxyacetic acid hydrazide (VIIc)

A solution of VIc (0.61 g, 0.001 mol) in ethanol (6 ml) was refluxed with hydrazine hydrate (0.6 ml) for 10 hr. The reaction mixture was concentrated and the residue triturated with water. The solid thus obtained was filtered washed with water and dried to give VIIc, yield 0.49 g (82%), m.p. 152°; PMR: 2.37 (*bs*, 6H, $2 \times COCH_3$), 3.77 (*s*, 3H, OCH_3), 3.80 (*s*, 3H, OCH_3), 4.77 (*s*, 2H, OCH_2CO) (Found: C, 63.9; H, 6.0; N, 13.8. $C_{32}H_{34}N_6O_6$ requires C, 64.2; H, 5.7; N, 14.0%).

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